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(54) Title: SUBSTITUTED DIPEPTIDE ANALOGS PROMOTE RELEASE OF GROWTH HORMONE

(57) Abstract

There are disclosed certain novel compounds identified as substituted dipeptide analogs which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such substituted dipeptide analogs as the active ingredient thereof are also disclosed.

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TITLE OF THE INVENTION

SUBSTITUTED DIPEPTIDE ANALOGS PROMOTE RELEASE OF GROWTH HORMONE

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic process of the body:

1. Increased rate of protein synthesis in all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering an agent which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth

hormone. Recently, recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

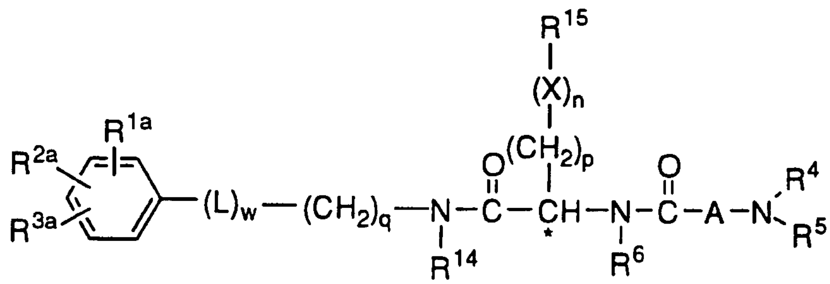
Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. The instant compounds are highly substituted dipeptide analogs for promoting the release of growth hormone which are stable under various physiological conditions which may be administered parenterally, nasally or by the oral route.

SUMMARY OF THE INVENTION

The instant invention covers certain substituted dipeptide analogs which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the diphenyl substituted dipeptide analogs. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the substituted dipeptide analogs for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

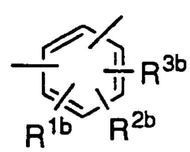
DESCRIPTION OF THE INVENTION

The novel substituted dipeptide analogs of the instant invention are best described in the following structural formula I:



I

where L is



n is 0 or 1;
p is 0 to 6;
q is 0 to 4;
w is 0 or 1;

$$X \text{ is } C{=}O,\ O,\ S(O)_m,\ \text{-}\overset{\displaystyle OH}{\overset{|}{C}}H\text{-},\ \text{-}\overset{\displaystyle R10}{\overset{|}{N}}\text{-},\ \text{-}CH{=}CH\text{-};$$

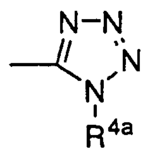
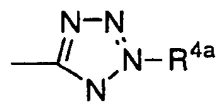
m is 0 to 2;

R1, R2, R1a, R2a, R1b, and R2b are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_3 perfluoroalkoxy, -$S(O)_m$-R7a, cyano, nitro, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO$-$(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, R^4R^5-$NCOO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy; R7a

and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy and v is 0 to 3;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is


, 
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$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^{7b}O(CH_2)_vCO$-, $R^{4b}R^{12c}N(CH_2)_v$-, $R^{12a}R^{12b}NCO(CH_2)_v$-, $R^{12a}R^{12b}NCS(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CO(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CS(CH_2)_v$-, $R^{4b}R^{12a}NCON(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NCSN(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CON(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CSN(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})$-$COO(CH_2)_v$-, $R^{4b}R^{12a}NCOO(CH_2)_v$-, or $R^{13}OCON(R^{12c})(CH_2)_v$-, where v is 0 to 3;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}, OR^{5a}, or COR^{5a}; R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{12a} and R^{12c}, or R^{4b} and R^{12a}, or R^{4b} and R^{12a}, or R^{4b} and R^{12c}, or R^{13} and R^{12c}, can be taken together to form $-(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 3 and R^1 and R^{10} are as defined;

R^{13} is C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are hydroxy, $-NR^{10}R^{11}$, carboxy, phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents

on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy where R^{10} and R^{11} are as defined;

R^{14} is hydrogen, R^1, R^2 independently disubstituted phenyl, C_1-C_{10} alkyl or substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl, C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl C_1-C_5 alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl or $-NR^{10}R^{11}$ where R^1, R^2, R^{10} and R^{11} are as defined;

R^{15} is hydrogen, trifluoromethyl, R^1, R^2 independently disubstituted phenyl, R^1, R^2 independently disubstituted naphthyl, C_3-C_7 cycloalkyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted naphthyl, R^1, R^2 independently disubstituted naphthyl C_1-C_3 alkoxy, C_1-C_5 alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ or R^1, R^2 independently disubstituted heterocycle, where the heterocycle is imidazole, thiophene, furan, pyrrole, oxazole, thiazole, triazole, tetrazole, pyridine, benzofuran, benzothiophene, benzimidazole, indole, 7-azaindole, oxindole or indazole; where R^1, R^2, R^{10} and R^{11} are as defined above;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_3-C_{10} alkenyl, substituted C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, or substituted C_3-C_{10} alkynyl where the substituents on the phenyl, alkyl, alkenyl or alkynyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, fluoro, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, phenyl, phenyl C_1-C_6 alkyl,

C_1-C_5-alkoxycarbonyl, C_1-C_5-alkanoyl or C_1-C_6 alkyl; or R^4 and R^5 can be taken together to form -$(CH_2)_rB(CH_2)_s$- where B, r, s, R^1 and R^{10} are as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl, phenyl or phenyl C_1-C_{10} alkyl;

A is

$$—(CH_2)_x—\underset{\substack{| \\ R^{8a}}}{\overset{\substack{R^8 \\ |}}{C}}—(CH_2)_y—$$

where x and y are independently 0-3;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, trifluoromethyl, phenyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or -$NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above; or R^8 and R^{8a} can be taken together to form -$(CH_2)_t$- where t is 2 to 6; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or

branched configuration. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Preferred compounds of the instant invention are realized when in the above structural formula:

n is 0 or 1;
p is 0 to 4;
q is 0 to 2;
w is 0 or 1;

$$\text{X is O, } S(O)_m, \overset{\displaystyle R^{10}}{\underset{}{\overset{|}{\text{-N-}}}}, \text{-CH=CH-;}$$

m is 0 to 2;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl; phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is as defined above;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}, OR^{5a}, or COR^{5a}; R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form $-(CH_2)_r-B-(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 3, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl, phenyl C_1-C_6 alkyl or C_1-C_5 alkanoyl-C_1-C_6 alkyl;

R^{13} is C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are hydroxy, $NR^{10}R^{11}$, carboxy, phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^{14} and R^{15} are as defined above;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl or phenyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy or formyl;

R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or N-R^{10}, r and s are independently 1 to 3 and R^1 and R^{10} are as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl or phenyl C_1-C_{10} alkyl;

A is

$$-(CH_2)_x-\overset{\displaystyle R^{8}}{\underset{\displaystyle R^{8a}}{\overset{|}{\underset{|}{C}}}}-(CH_2)_y-$$

where x and y are independently 0-2;

R^8, R^{8a} and R^{8b} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, or C_1-C_5 alkanoyl-C_1-C_6 alkyl; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2 to 4; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

Additional preferred compounds are realized in the above structural formula when:

n is 0 or 1;
p is 0 to 3;
q is 0 to 2;
w is 0 or 1;
X is O, $S(O)_m$ or -CH=CH-;
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is as defined above;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a} or OR^{5a}. R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form -$(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 2, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl or C_1-C_5 alkanoyl-C_1-C_6 alkyl;

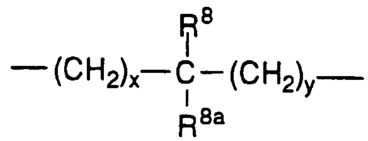
R^{13} is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^{14} and R^{15} are as defined above;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl or carboxy;

R^6 is hydrogen or C_1-C_{10} alkyl;

A is



where x and y are independently 0-2;

R^8, R^{8a} and R^{8b} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2; or R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

Still further preferred compounds of the instant invention are realized in the above structural formula when;
n is 0 or 1;
p is 0 to 2;
q is 1;
w is 1;
X is O, $S(O)_m$;
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 or 1;

R^{3a} and R^{3b} are independently hydrogen, R^9, or C_1-C_6 alkyl substituted with R^9;

R^9 is as defined above;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}. R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form $-(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 2, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl or C_1-C_5 alkanoyl C_1-C_6 alkyl;

R^{13} is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^{14} and R^{15} are as defined above;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 3 of hydroxy, C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20} alkanoyloxy, C_1-C_5 alkoxycarbonyl or carboxy;

R^6 is hydrogen;

A is

$$-(CH_2)_x-\overset{\displaystyle R^8}{\underset{\displaystyle R^{8a}}{\overset{|}{\underset{|}{C}}}}-(CH_2)_y-$$

where x and y are independently 0-1;

R^8, R^{8a} and R^{8b} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

Representative preferred growth hormone releasing compounds of the present invention include the following:

1. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide

2. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]benzene-butanamide

3. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

4. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

5. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzenepentanamide

6. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]benzene-pentanamide

7. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

8. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

9. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

10. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-indole-3-propanamide

11. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

12. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

13. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

14. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[(phenyl-methyl)oxy]propanamide

15. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide

16. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide

17. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]-propanamide

18. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]-propanamide

19. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide

20. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

21. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-4-phenylbutyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

22. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-4-phenylbutyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

23. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

24. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

25. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-5-phenylpentyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

26. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-5-phenylpentyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

27. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-5-phenylpentyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

28. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-5-phenylpentyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

29. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

30. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

31. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

32. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-(1H-indole-3-yl)propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

33. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-[(phenylmethyl)oxy]propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

34. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-[(phenylmethyl)oxy]propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

35. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[(phenylmethyl)-oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

36. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[(phenylmethyl)-oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

37. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-[[(2,6-difluorophenyl)methyl]oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

38. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-[[(2,6-difluorophenyl)methyl]oxy]-propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

39. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[[(2,6-difluoro-phenyl)methyl]-oxy]propyl]amino]methyl]-N-ethyl-[1,1'-biphenyl]-2-carboxamide

40. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[[(2,6-difluoro-phenyl)methyl]-oxy]propyl]amino]methyl]-N-ethyl-[1,1'-biphenyl]-2-carboxamide

41. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

42. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

43. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

44. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

45. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

46. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

47. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

48. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

49. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

50. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

51. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

52. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

53. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide

54. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide

55. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

56. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

57. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

58. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

59. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

60. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino]-[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide

61. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide

62. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide

63. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

64. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

65. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzene-pentanamide

66. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzene-pentanamide

67. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

68. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

69. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

70. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

71. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

72. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

73. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

74. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

75. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide

76. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide

77. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

78. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

79. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

80. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

81. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

82. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

83. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzene-butanamide

84. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbon-yl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide

85. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

86. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

87. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzene-pentanamide

88. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbon-yl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]ben-zenepentanamide

89. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

90. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

91. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

92. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbon-yl]amino]-methyl][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

93. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-oxy]propanamide

94. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-oxy]propanamide

95. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide

96. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbon-yl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

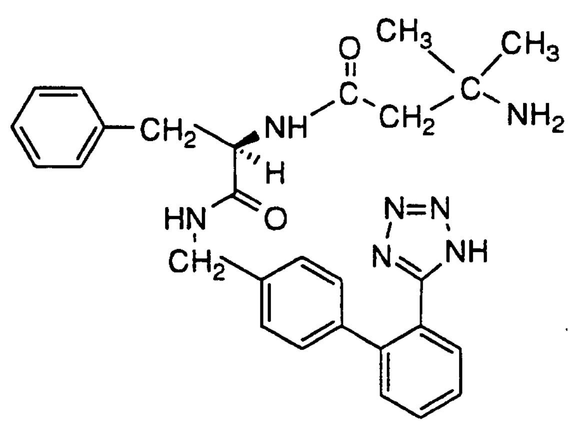
97. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluoro-phenyl)-methyl]oxy]propana-mide

98. (R)-α–[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluoro-phenyl)methyl]oxy]-propanamide

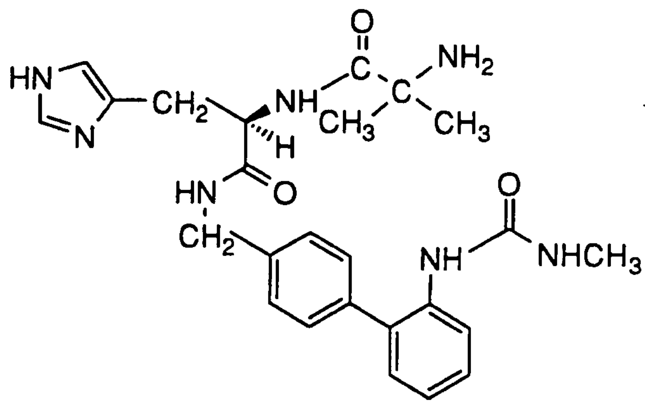
99. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

100. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbon-yl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

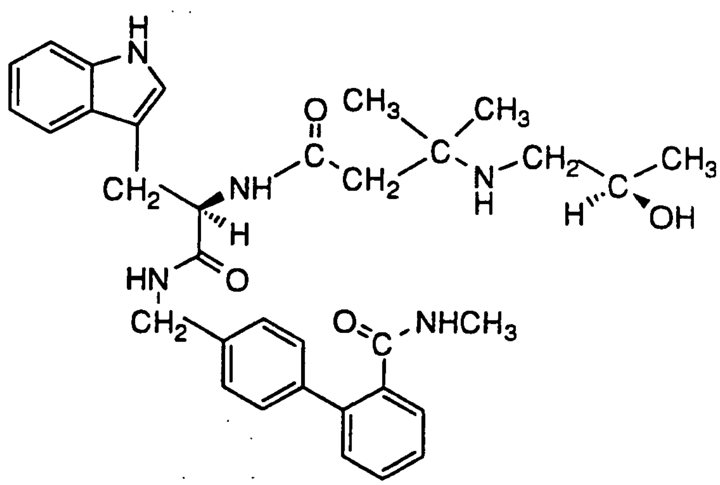
Representative examples of the nomenclature employed are given below:



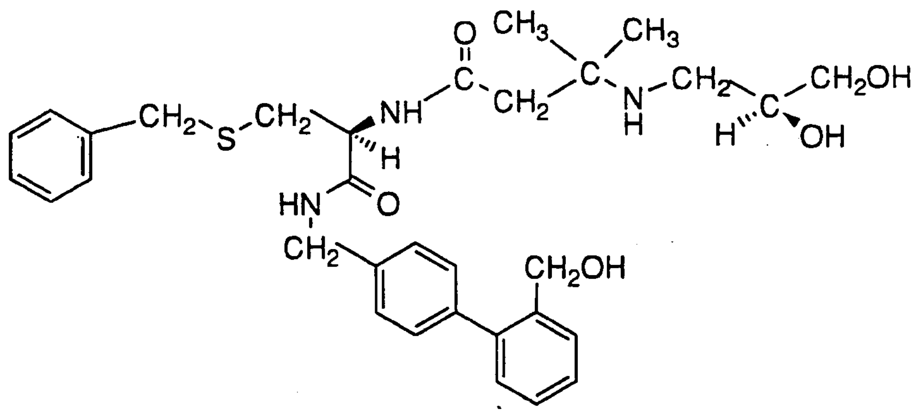
(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepropanamide



(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]-methyl]-1H-imidazole-4-yl-propanamide

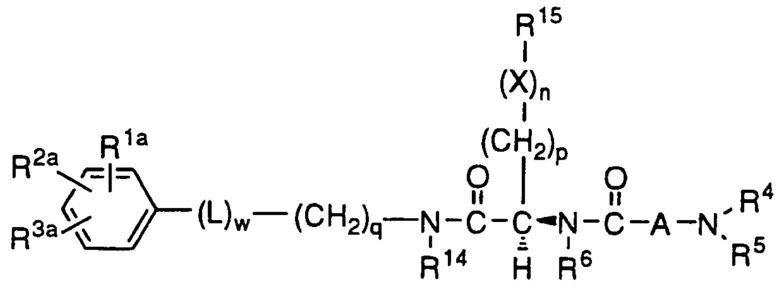


(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]-methyl]-N-methyl[1,1'-biphenyl]-2-carboxamide



(S)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-thio]propanamide

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I above. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the compound in which the 3-amino substituent is above the plane of the structure, as seen in Formula Ia, is more active and thus more preferred over the compound in which the 3-amino substituent is below the plane of the structure. This center will be designated according to the R/S rules as either R or S depending upon the values of X, n, p and R^{15}.



Ia

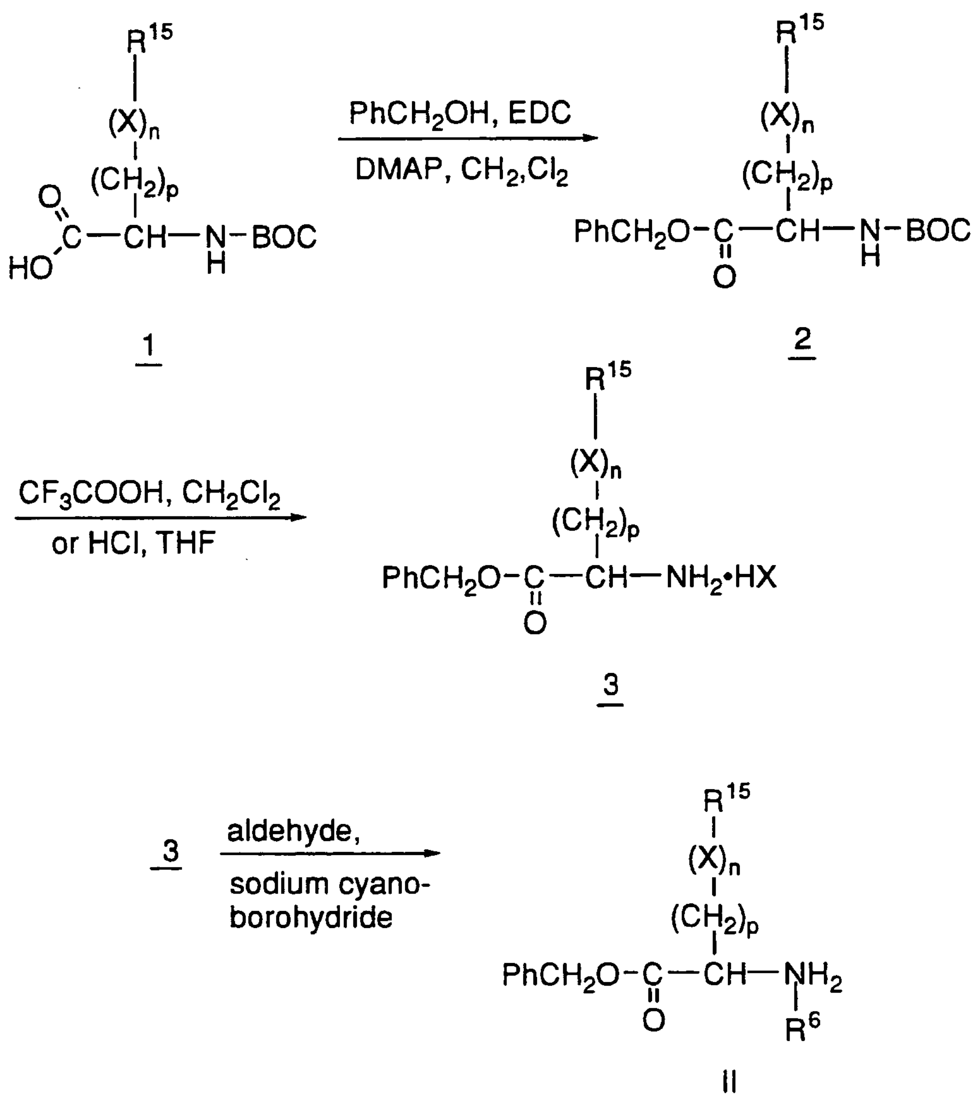
The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

Compounds I of the present invention are prepared from amino acid intermediates II as described in the following reaction schemes.

Amino acid intermediates 1 are, in some cases, commercially available in the form of their N-t-butoxycarbonyl or N-benzyloxycarbonyl derivatives. These intermediates can also be prepared by a variety of methods described in the literature and familiar to one skilled in the art. For example, the Strecker synthesis may be employed for the construction of racemic amino acid intermediates. Resolution can be achieved by classical methods, for example separation of diastereomeric salts by fractional crystallization. Alternatively, a chiral amino acid synthesis may be employed using the procedures described by R.M. Williams and M.N. Im (J. Amer. Chem. Soc., 113, 9276-9286, 1991.). Conversion of the free amino acid product to its N-t-butoxycarbonyl (BOC) derivative can be achieved by a number of methods known in the art, for example, treatment with di-

t-butyl dicarbonate in an inert solvent such as methylene chloride. Benzyloxycarbonyl (CBz) protected derivatives are obtained by treatment of the amino acid with, for example, benzyl chloroformate.

SCHEME 1

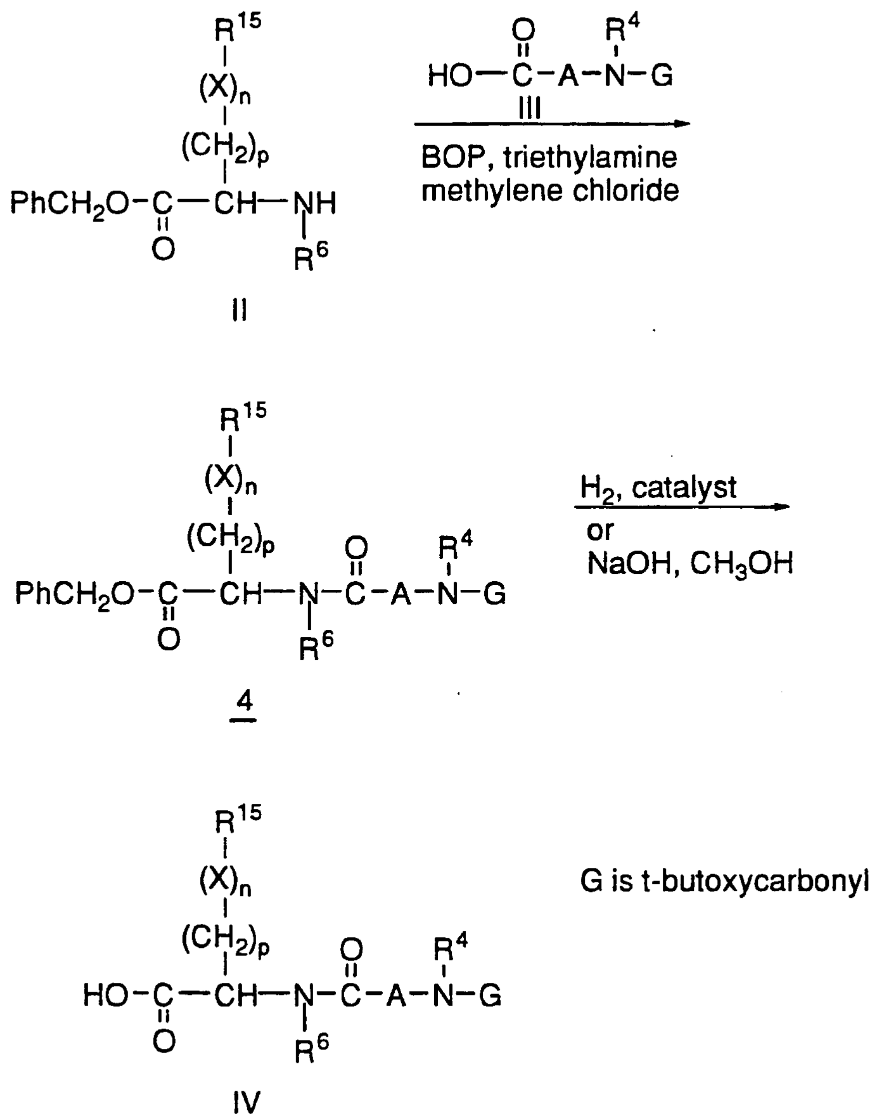


As shown in Scheme 1, formation of the benzyl ester 2 is carried out by treatment with benzyl alcohol in the presence of a coupling agent, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), in methylene chloride with a catalytic amount of

4-dimethylaminopyridine. Removal of the BOC protecting group through the use of trifluoroacetic acid in methylene chloride or hydrochloric acid in tetrahydrofuran gives the amine salt 3. Reductive alkylation with an aldehyde and a mild reducing agent, such as sodium cyanoborohydride, leads to the desired intermediate II.

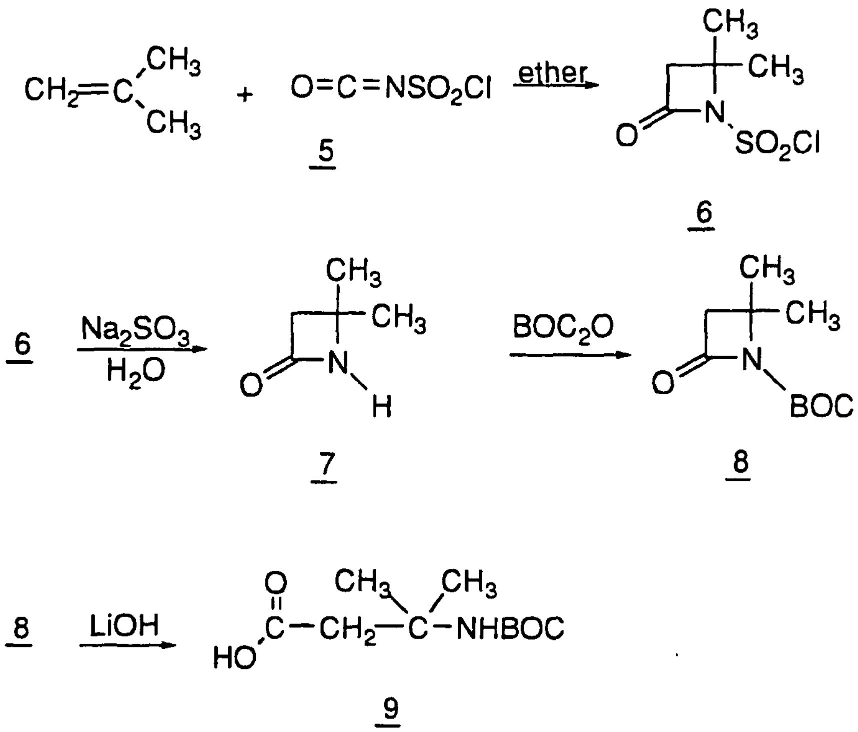
Attachment of the amino acid sidechain to intermediates of formula II is accomplished by the route shown in Scheme 2. Coupling is conveniently carried out by the use of an appropriately protected amino acid derivative, such as that illustrated by formula III, and a coupling reagent such as benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate ("BOP") in an inert solvent such as methylene chloride. Separation of unwanted side products, and purification of intermediates is achieved by chromatography on silica gel, employing flash chromatography (W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978)) or by medium pressure liquid chromatography. Removal of the benzyl ester by hydrogenolysis or by saponification in the presence of a strong base, such as sodium hydroxide, affords the product IV. It may be appreciated by one skilled in the art that the protecting group G must be selected to be compatible with the conditions employed for removal of the specific class of ester present in 4. Hence, as illustrated for the benzyl ester 4, G is taken as t-butoxycarbonyl. It may further be appreciated that other combinations of protecting group G and ester functionality may be employed; for example, the benzyloxycarbonyl protecting group is inert to the standard conditions of aqueous sodium hydroxide employed to hydrolyze methyl or ethyl esters.

SCHEME 2



The protected amino acid derivatives III are, in many cases, commercially available in t-butoxycarbonyl (BOC) or benzyloxy-carbonyl (CBz) forms. A useful method to prepare the preferred sidechain 9 is shown in Scheme 3.

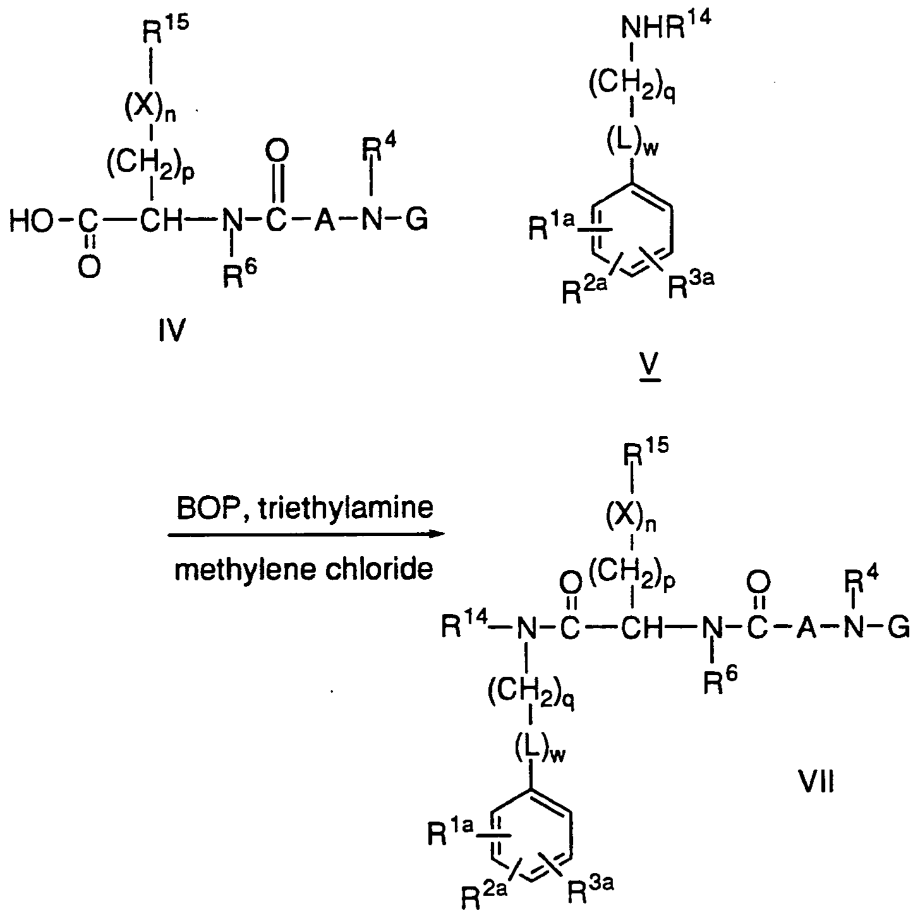
SCHEME 3



Reaction of isobutylene with N-chlorosulfonyl-isocyanate 5 in diethyl ether gives the azetidinone derivative 6. Removal of the chlorosulfonyl group with aqueous sodium sulfite followed by reaction with di-t-butyl-dicarbonate gives the BOC-protected intermediate 8. Alkaline hydrolysis gives the protected amino acid derivative 9 in good overall yield.

Attachment of the substituted phenyl sidechain V is achieved as shown in Scheme 4. Using the aforementioned BOP reagent, coupling is conveniently carried out in an inert solvent, such as methylene chloride, to give compounds of formula VII in protected form.

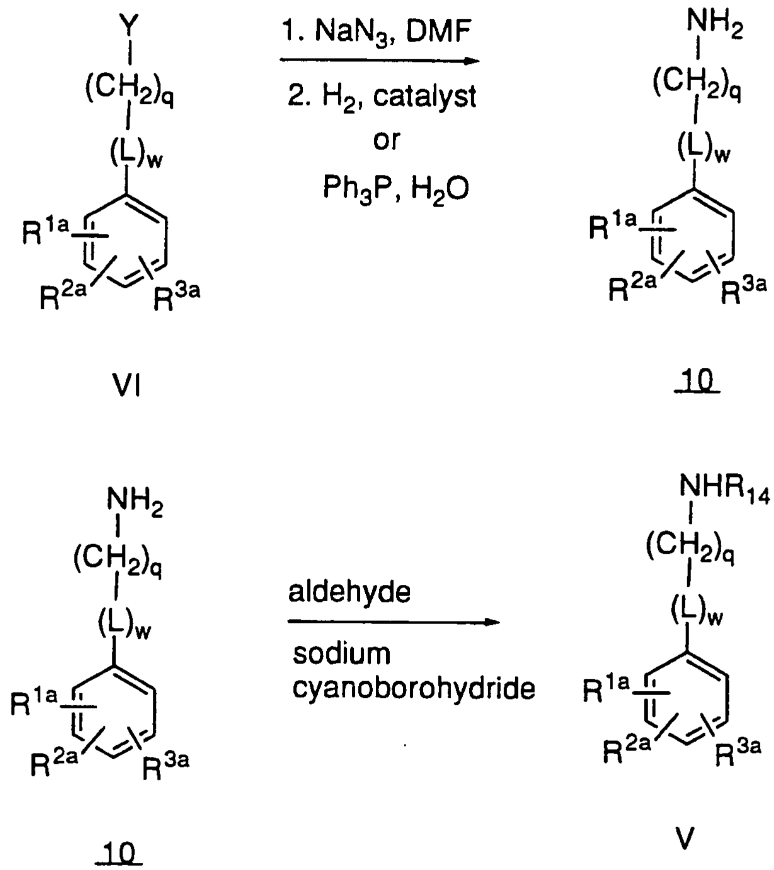
SCHEME 4



G is t-butoxycarbonyl or benzyloxycarbonyl

The substituted phenyl sidechains V are prepared from the corresponding alkylating agent VI by displacement of the leaving group Y with sodium azide as shown in Scheme 5. Reduction of the azide product by hydrogenation in the presence of a transition metal catalyst, or alternatively by reaction with triphenylphosphine followed by hydrolysis, gives the desired amine derivative 10. Conversion to the desired intermediate V is achieved by the aforementioned reductive alkylation procedure.

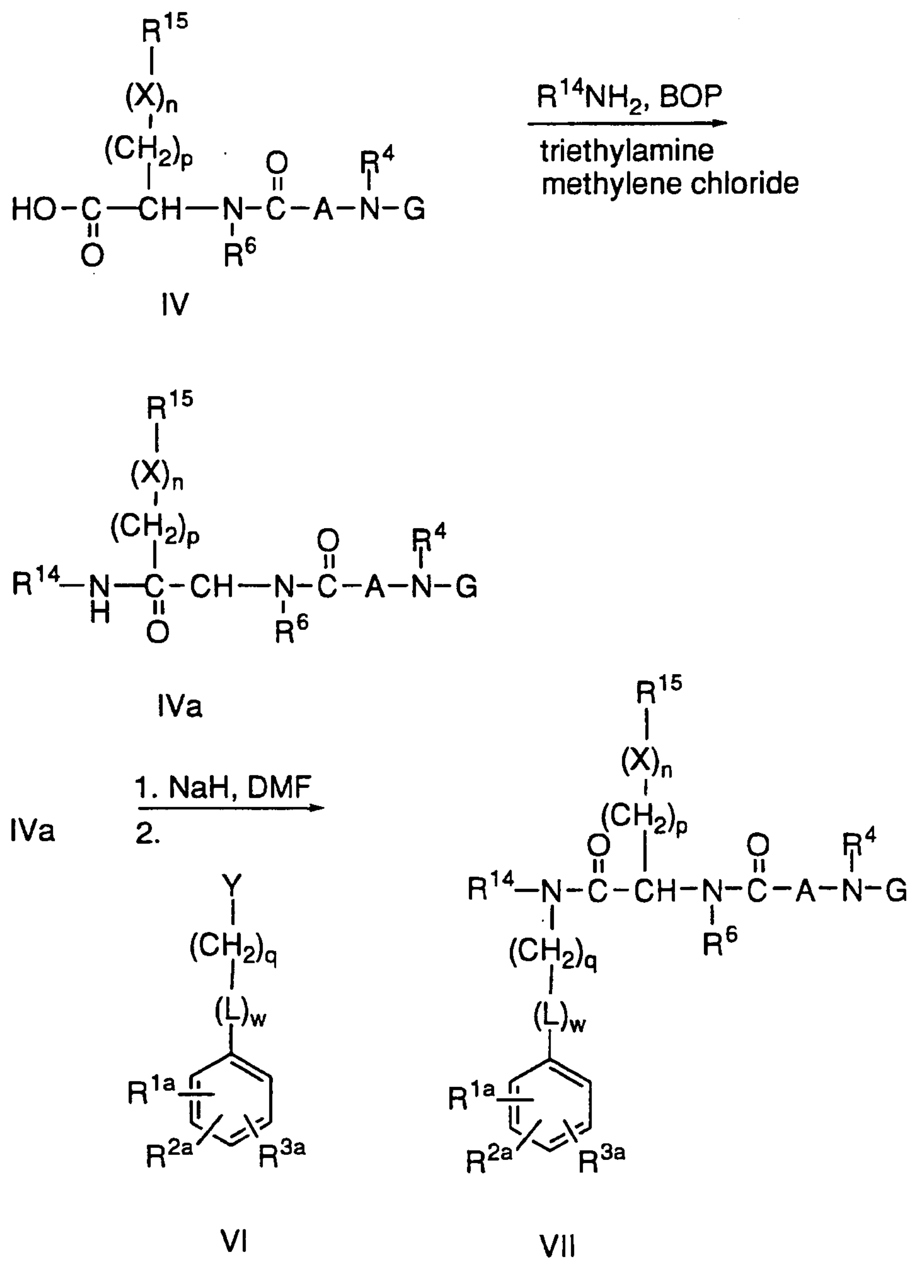
SCHEME 5



Y is a leaving group

As illustratrated in Scheme 6 an alternative route involves coupling of intermediate IV with $R^{14}NH_2$ using one of the coupling reagents described previously, followed by alkylation of the amide bond with VI. Alkylation is carried out in an inert solvent, such as dimethylformamide, using a strong base such as sodium hydride or potassium t-butoxide at temperatures of 0°-100°C. Alkylating agents VI are, in some cases, commercially available or may be prepared by the procedures described in the following schemes.

SCHEME 6

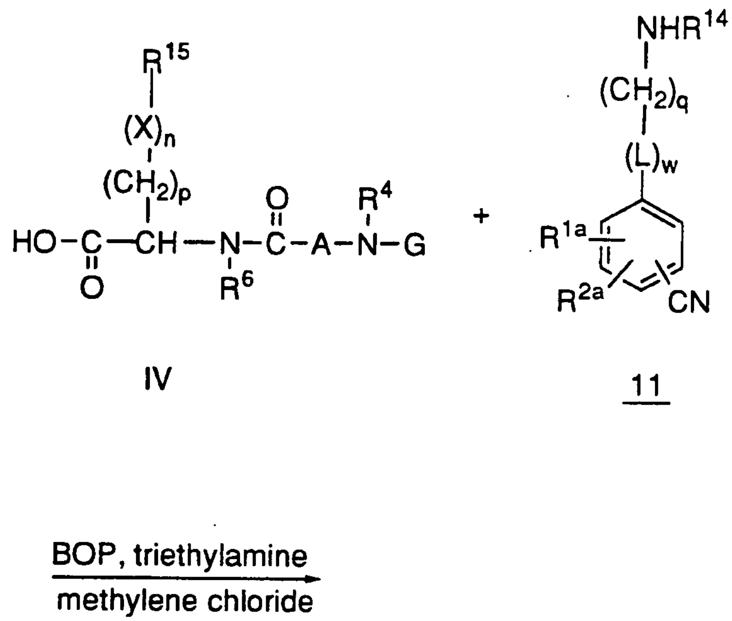


G is t-butoxycarbonyl or benzyloxycarbonyl

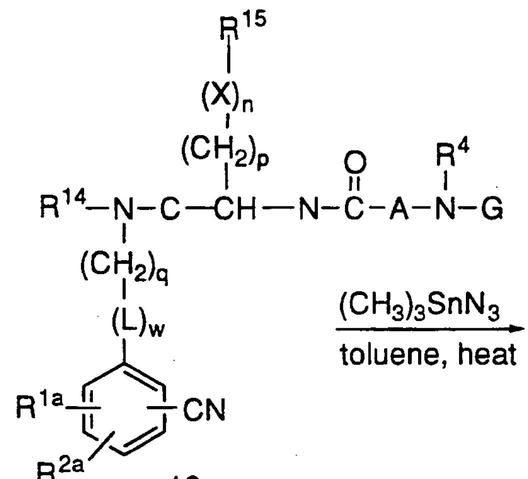
Alkylating agents VI are, in some cases commercially available compounds or may be prepared by methods described in the literature and familiar to one skilled in the art.

Compounds of formula I wherein R^{3a} or R^{3b} is a tetrazole (13) are prepared as described in Scheme 7 by reaction of IV with a suitably substituted intermediate 11 containing a nitrile as tetrazole precursor. Elaboration to the desired product 13 is carried out by treatment with trimethyltin azide in boiling toluene.

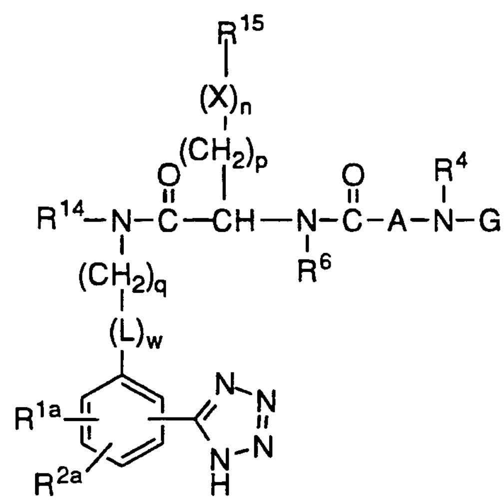
SCHEME 7



SCHEME 7 (cont'd)



12

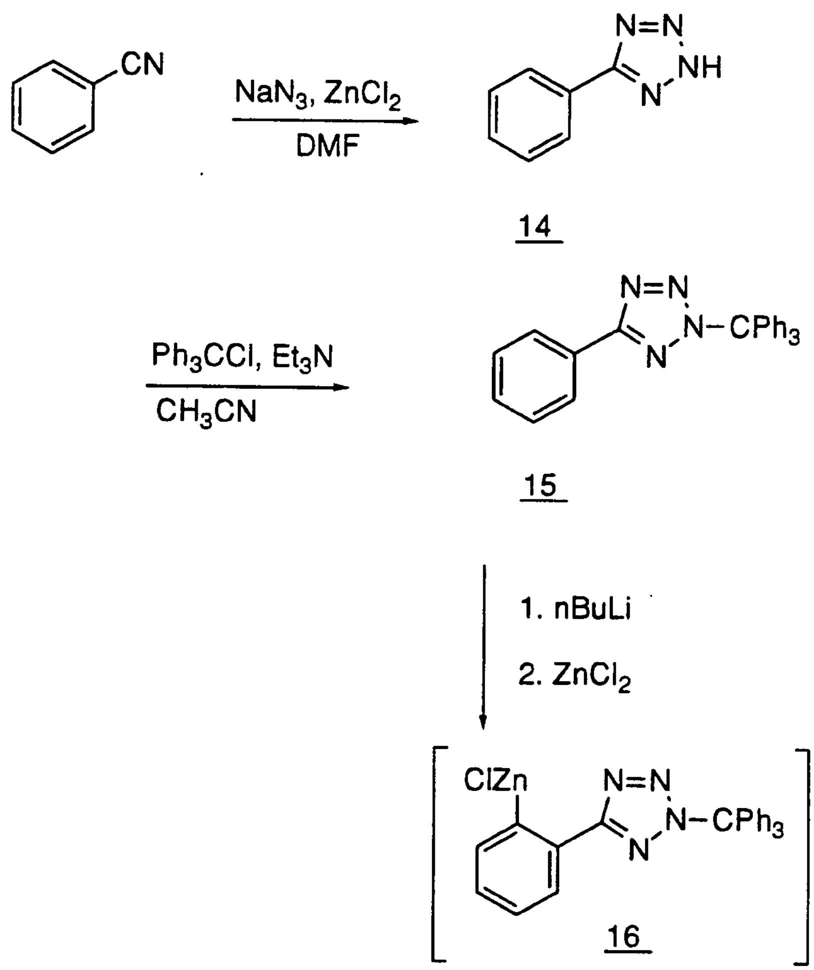


13

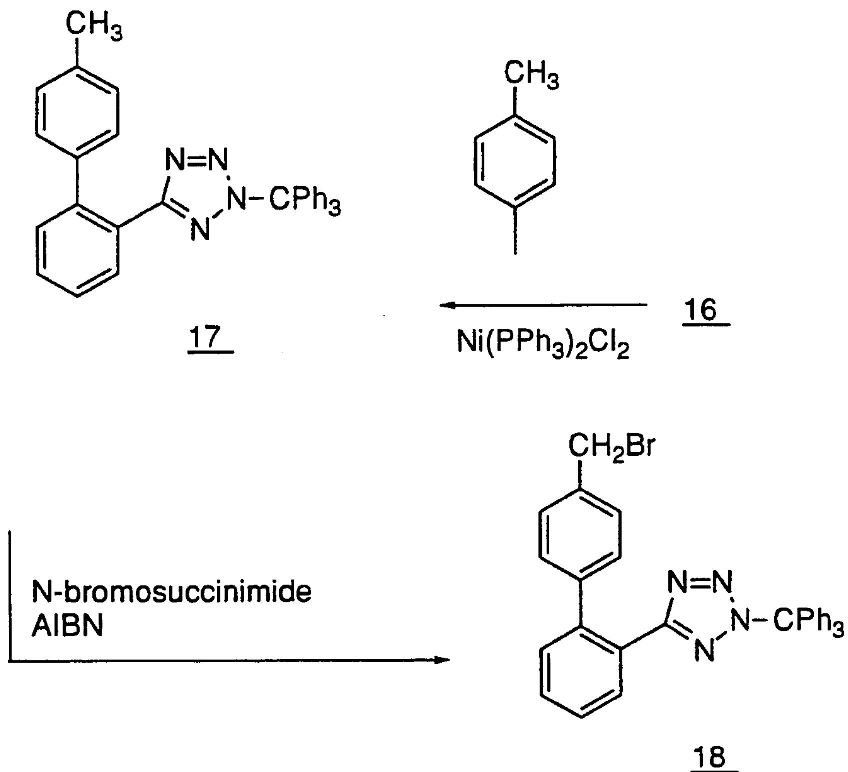
G=t-butoxycarbonyl or benzyloxycarbonyl

A useful method to prepare the preferred intermediate 18 is shown in Scheme 8, and in U.S. Patent 5,039,814.

SCHEME 8



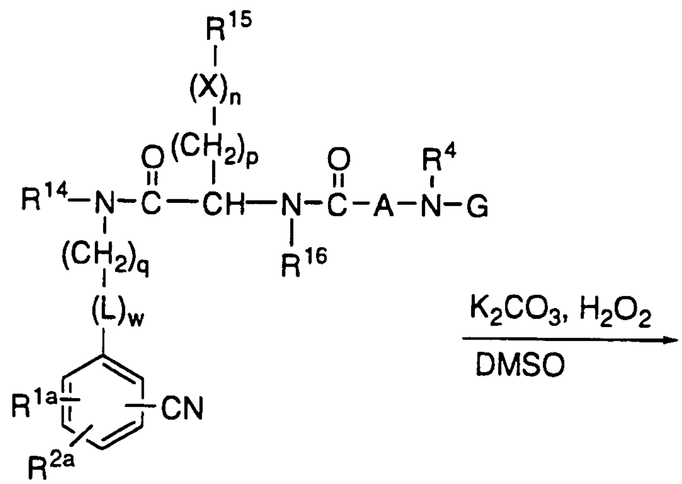
SCHEME 8 (cont'd)



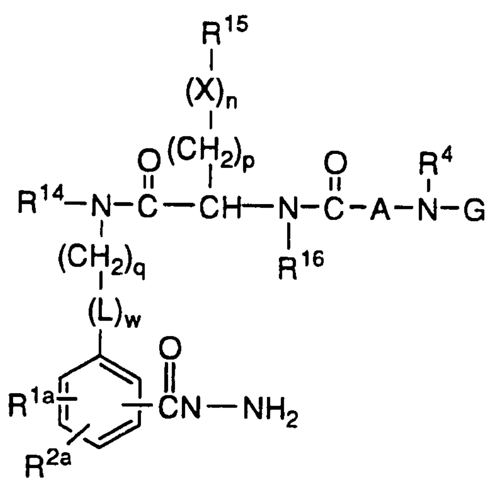
As outlined in Scheme 8, benzonitrile is treated with sodium azide and zinc chloride to give 5-phenyltetrazole 14 which is converted to the N-trityl derivative 15 by treatment with triphenyl-methyl chloride and triethylamine. The zinc reagent 16 was prepared by treatment with n-butyl lithium followed by zinc chloride. Coupling with 4-iodotoluene using the catalyst bis(triphenylphosphine)nickel(II) dichloride gives the biphenyl product 17 in high yield. Reaction with N-bromosuccinimide and AIBN gives bromide 18. Conversion to the requisite amine derivative V is achieved by the procedure described in Scheme 5.

Compounds of Formula I wherein R^{3a} or R^{3b} are taken as R^4R^5NCO can be prepared by several methods. For example, as shown in Scheme 9, compound 20 wherein R^4 and R^5 are both hydrogen is conveniently prepared by hydrolysis of a nitrile precursor 19.

SCHEME 9



19

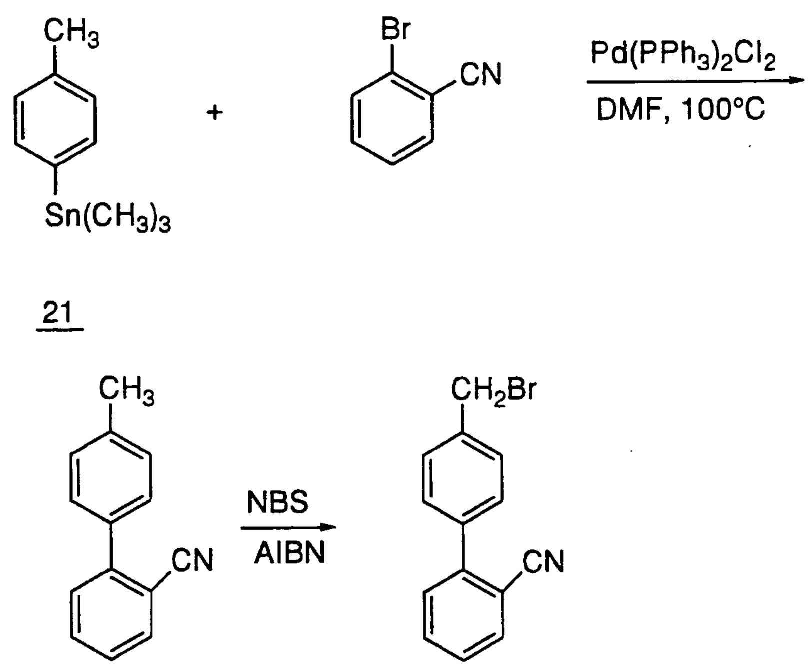


20

Thus, treatment of the nitrile 19 with hydrogen peroxide and a strong base, such as potassium carbonate, in a polar solvent, such as dimethylsulfoxide at temperatures of 25°C to 150°C results in formation of the amide derivative 20.

A useful method of preparing the intermediate 23 is outlined in Scheme 10.

SCHEME 10

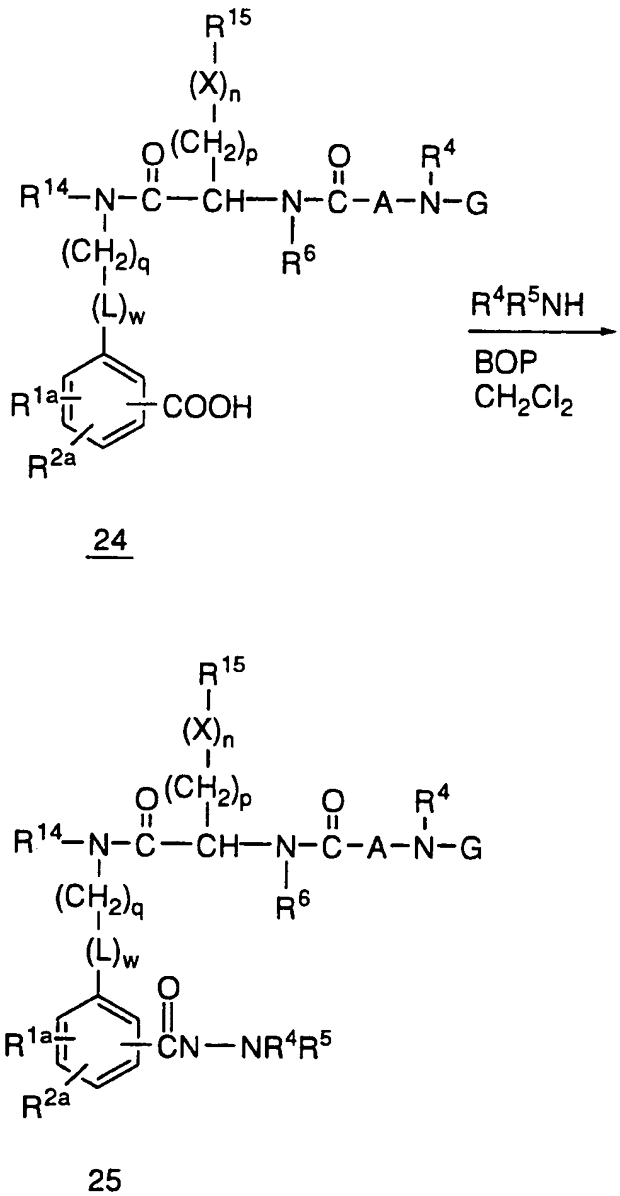


21 22 23

Thus, treatment of 4-(methylphenyl)trimethyl stannane 21 with 2-bromobenzonitrile in dimethylformamide at 100°C in the presence of bis-triphenylphosphine palladium (II) chloride results in coupling to form the biphenyl nitrile 22 in high yield. Conversion to bromide 23 is achieved by treatment with N-bromosuccinimide and a radical initiator, such as azobisisobutyronitrile (AIBN), in refluxing carbon tetrachloride. Conversion to the requisite amine derivative V is achieved by the procedure described in Scheme 5.

Compounds of Formula I wherein R^{3a} or R^{3b} are taken as R^4R^5NCO and R^4 and/or R^5 are other than hydrogen are prepared from the corresponding carboxylic acid derivatives 24 as shown in Scheme 11.

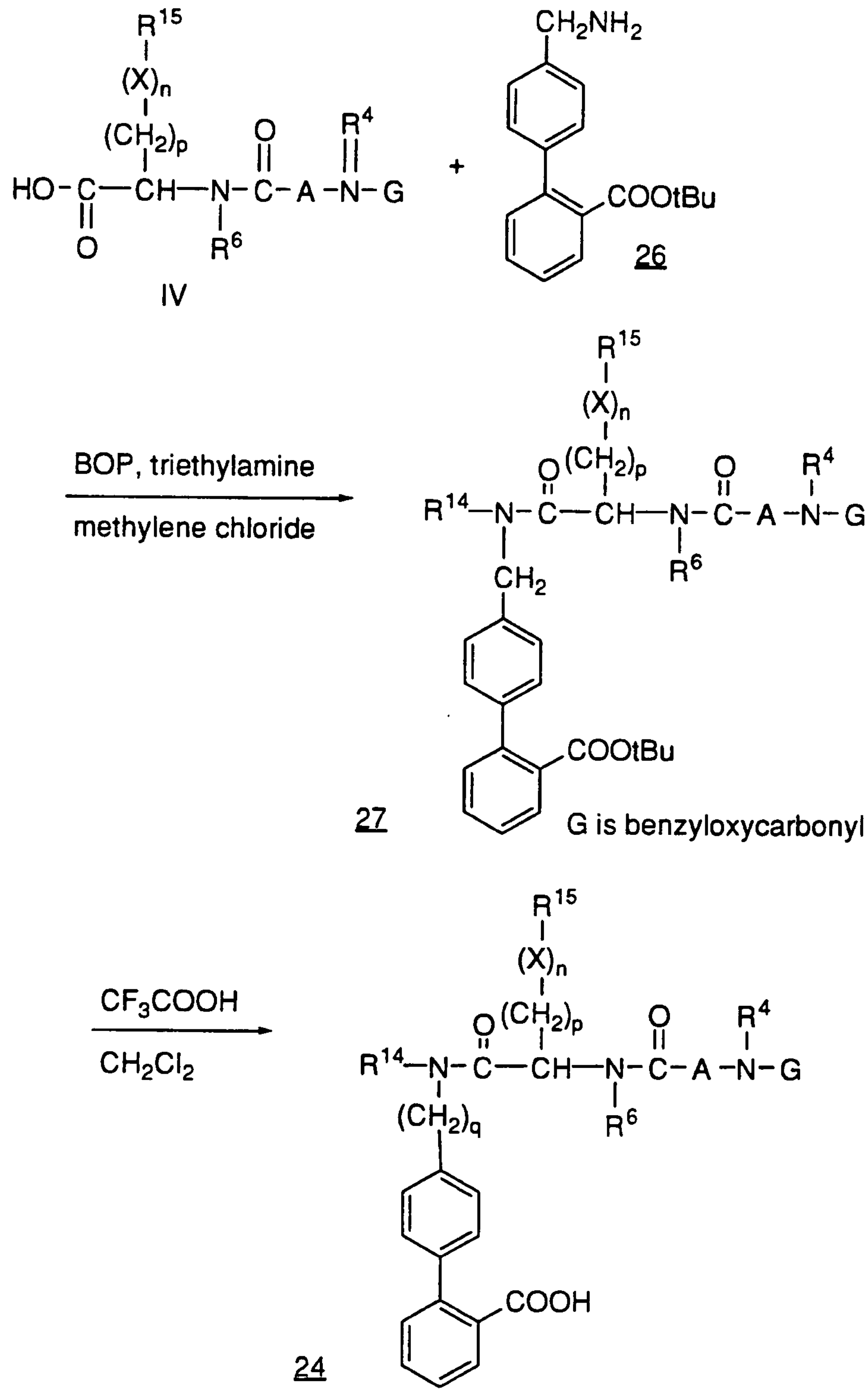
SCHEME 11



Coupling of the carboxylic acid derivative 24 with R^4R^5NH is conveniently carried out by the use of a coupling reagent such as benzotriazol-l-yloxytris-(dimethylamino)phosphonium hexafluorophosphate ("BOP") in an inert solvent such as methylene chloride.

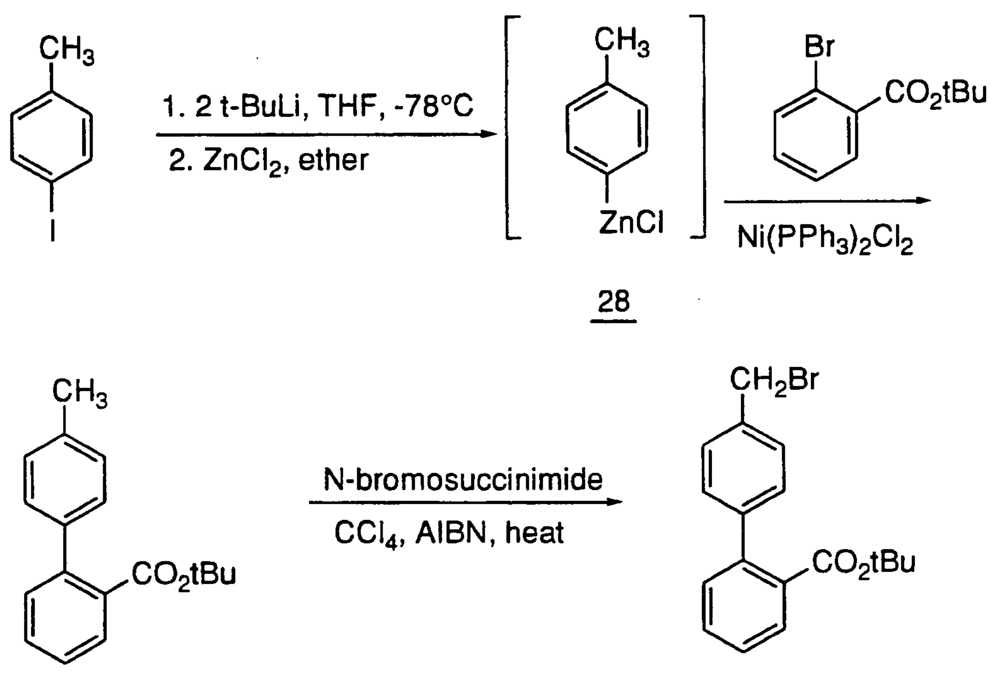
The requisite carboxylic acid precursors can be prepared as illustrated in Scheme 12 for the biphenyl compound <u>24</u>.

SCHEME 12


R15
(X)n
(CH2)p
O
R4
HO-C—CH—N-C-A-N-G
O
R6
IV
+
CH2NH2
COOtBu
26
BOP, triethylamine
methylene chloride
R15
(X)n
O (CH2)p
O
R4
R14—N-C—CH—N-C-A-N-G
CH2
R6
COOtBu
27
G is benzyloxycarbonyl
CF3COOH
CH2Cl2
R15
(X)n
O (CH2)p
O
R4
R14—N-C—CH—N-C-A-N-G
(CH2)q
R6
COOH
24

A convenient method to prepare the useful intermediate 30 is shown in Scheme 13. Metallation of 4-iodotoluene with t-butyllithium in tetrahydro-furan, followed by treatment with zinc chloride gives the intermediate zinc reagent 28. Coupling of 28 with t-butyl 2-bromobenzoate in the presence of bis(triphenylphosphine)nickel(II) chloride affords the biphenyl product 29 in high yield. Bromination to give the desired intermediate 30 is carried out under the aforementioned conditions. Conversion to the requisite amine derivative V is achieved by the procedure described in Scheme 5.

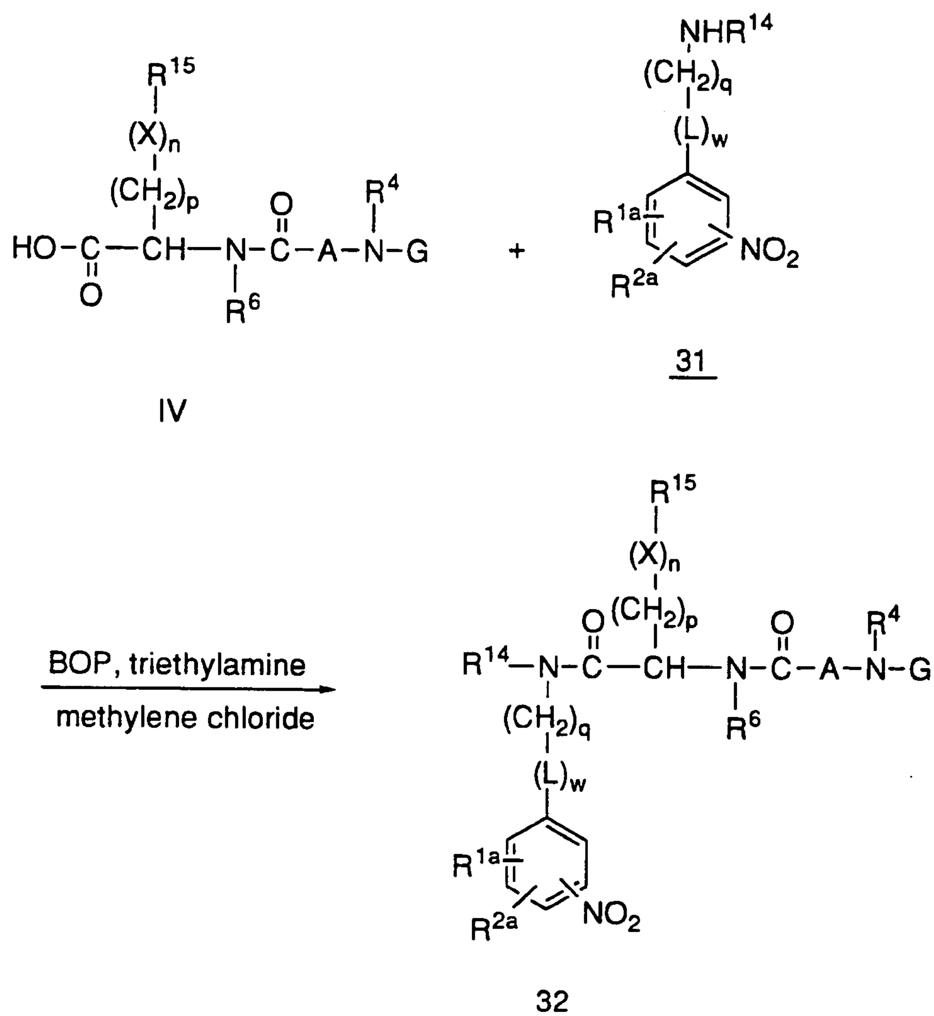
SCHEME 13



29 30

Compounds of formula I where R^{3a} or R^{3b} is a carbamate, semicarbazide or urea derivative, wherein this functionality is attached to the phenyl ring by a nitrogen atom are prepared from intermediate 32, obtained by reaction with a derivative 31 wherein R^{3a} or R^{3b} is a nitro group as shown in Scheme 14.

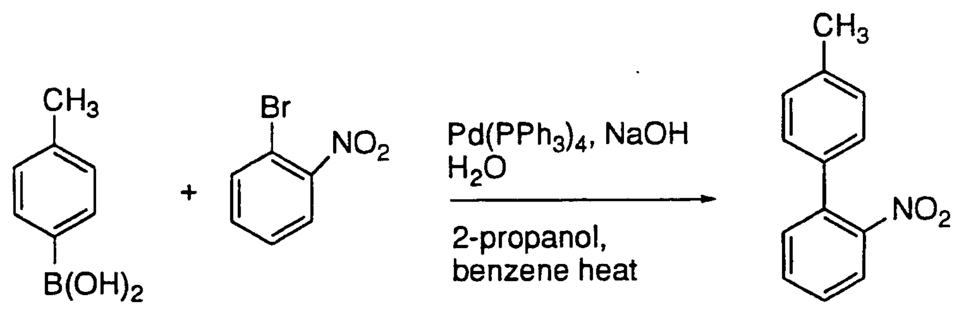
SCHEME 14



G is t-butoxycarbonyl

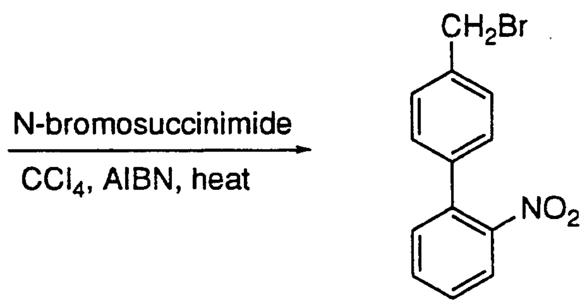
A useful method of synthesizing a preferred intermediate 36 is shown in reaction Scheme 15.

SCHEME 15



33 34 35

35



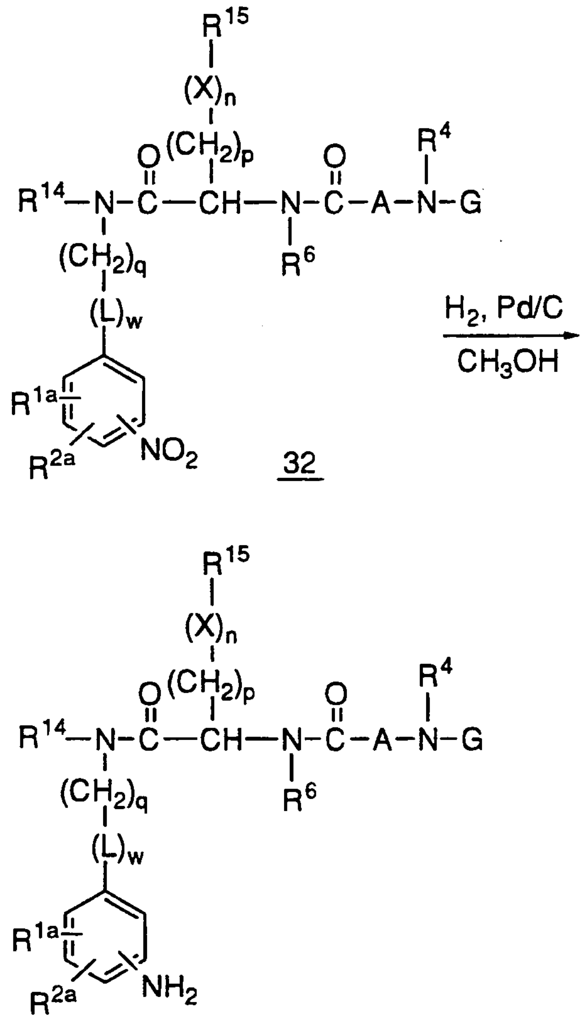
36

Reaction of 4-tolylboronic acid 33 with 2-bromonitrobenzene 34 in the presence of a transition metal catalyst such as (tetrakis)triphenylphosphine palladium (O) in a mixed solvent system containing aqueous sodium hydroxide, water, 2-propanol and benzene at elevated temperatures for several hours gives the coupled product 35 in good overall yield. Chromatographic purification and separation of unwanted by-products is conveniently performed on silica, eluting with common organic solvents such as hexane, ethyl acetate and methylene chloride. Conversion of 35 to the bromide derivative 36 is accomplished by treatment with N-bromosuccinimide in refluxing carbon tetrachloride in the presence of a radical initiator such as benzoyl peroxide or 2,2-azobisisobutyronitrile (AIBN). Conversion to

the requisite amine derivative V is acheived by the procedure described in Scheme 5.

As shown in Scheme 16, reduction of the nitro group of 32 is achieved by hydrogenation in the presence of a metal catalyst, such as palladium on carbon, in a protic solvent such as methanol or ethanol. It may be appreciated by one skilled in the art that for certain compounds where catalytic hydrogenation is incompatible with existing functionality, alternative methods of reduction are indicated, such as chemical reduction with stannous chloride under acidic conditions. It should also be noted that the protecting group G in intermediate 32 must be compatible with the experimental conditions anticipated for reduct-ion. For example, intermediate 32 wherein G is t-butoxycarbonyl (BOC) are stable to the conditions of catalytic reduction employed in the conversion to 37. Intermediate 37 may also be further elaborated to new intermediate 38 by reductive alkylation with an aldehyde by the aforementioned procedures.

SCHEME 16

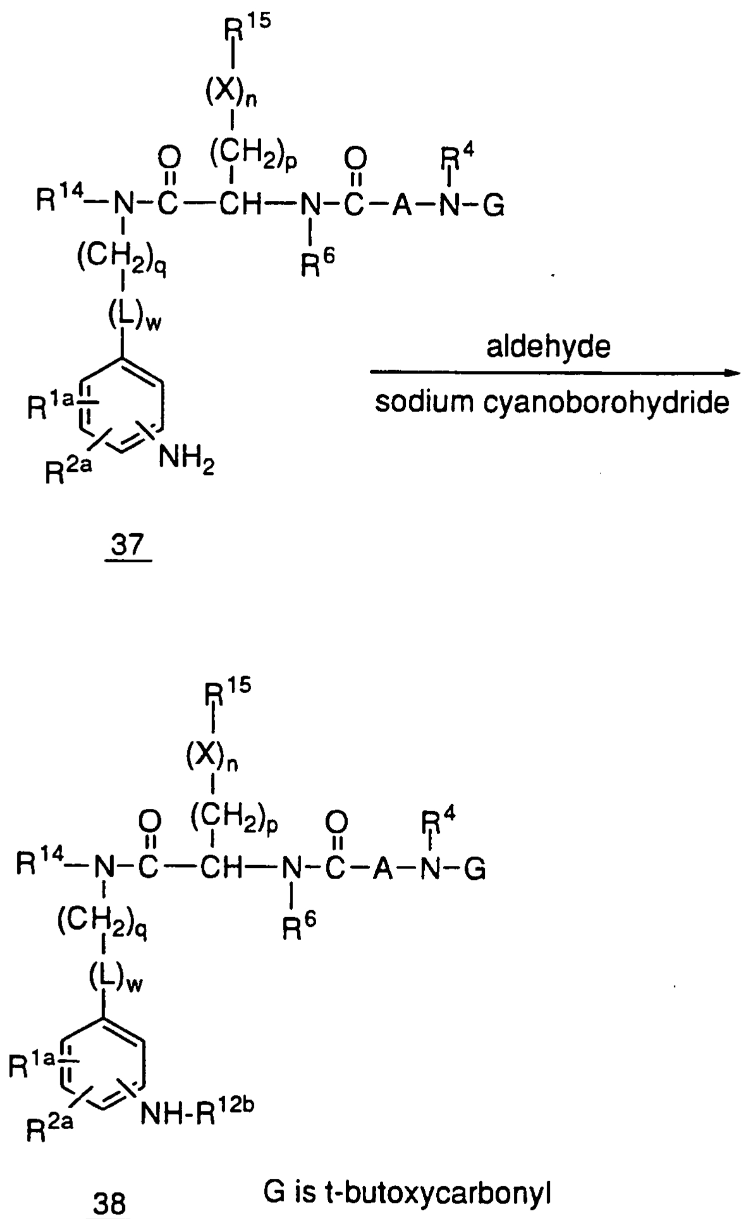


32

37

G is t-butoxycarbonyl

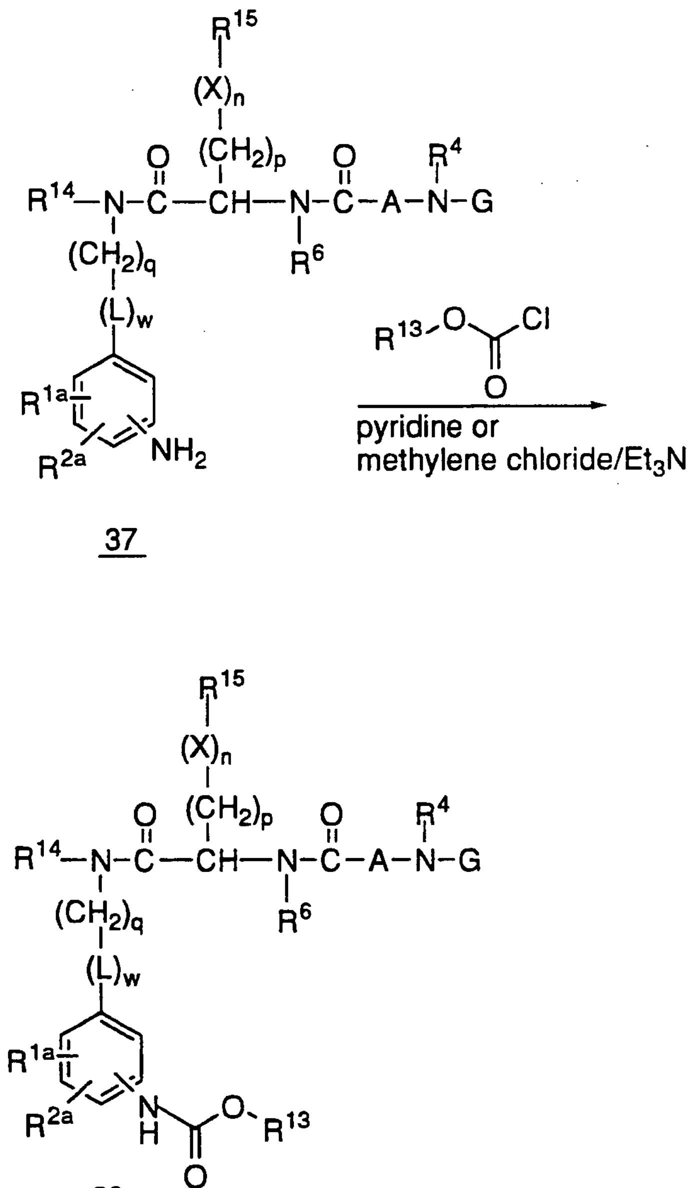
SCHEME 16 (cont'd)



G is t-butoxycarbonyl

Elaboration of 37 to carbamate compounds is achieved by reaction with the appropriate chloroformate reagent in pyridine or in methylene chloride with triethylamine as shown in Scheme 17.

SCHEME 17



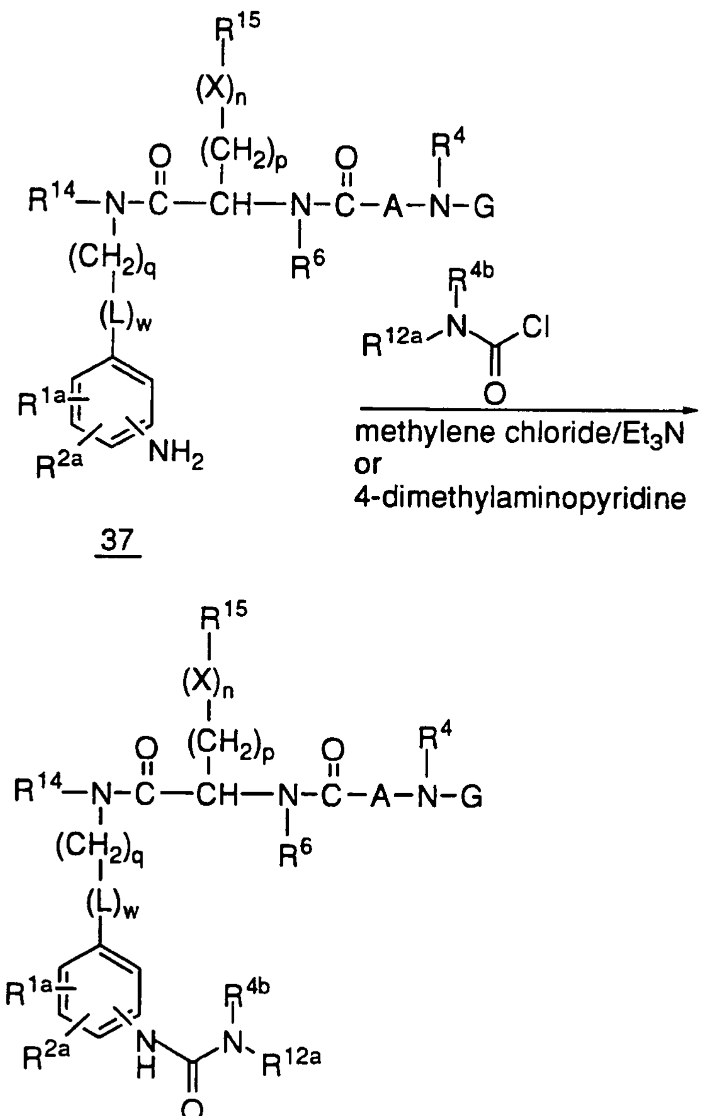
37

39

Transformation of amine intermediate 37 to urea derivatives is accomplished in several ways. Terminally disubstituted compounds 40 can be obtained directly by reaction of 37 with a disubstituted carbamoyl chloride in an inert solvent such as methylene chloride in the presence of triethylamine or 4-dimethylaminopyridine.

In addition, monosubstituted compounds 41 wherein either R^{4b} or R^{12a} is hydrogen are obtained from 37 by reaction with an isocyanate as shown in Scheme 18.

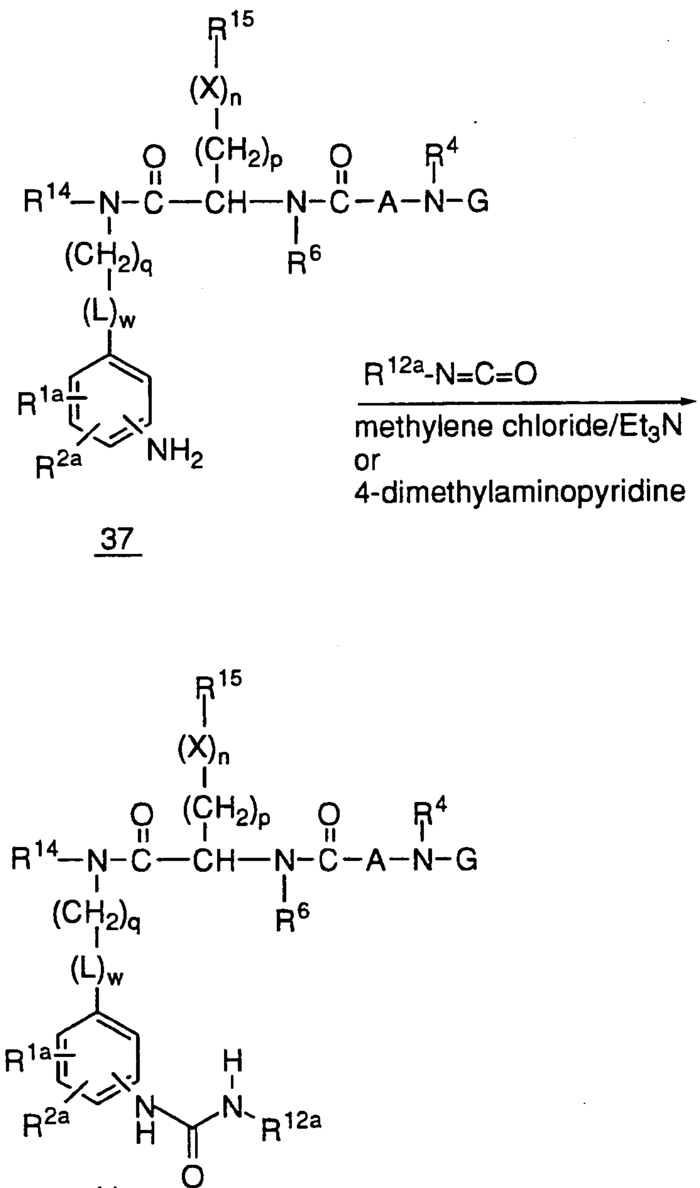
SCHEME 18



37

40

SCHEME 18 (cont'd)



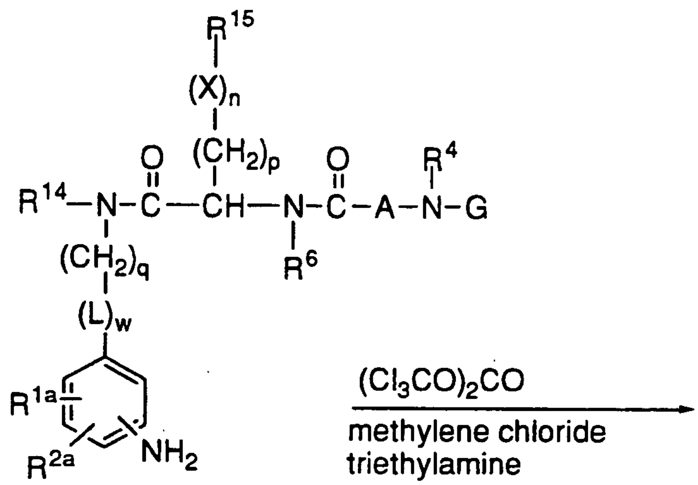
37

41

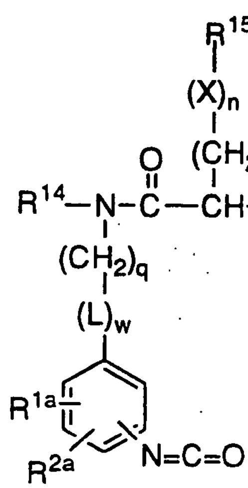
Alternatively, amine 37 is converted to an isocyanate 42 by treatment with phosgene or an equivalent reagent such as bis(trichloromethyl)carbonate (triphosgene) as indicated in Scheme 19. Subsequent reaction of 42 with primary or secondary amines in an inert solvent

such as methylene chloride gives the corresponding urea derivates 43 in good yield. Isocyanate 42 is also converted to substituted semi-carbazides 44 or hydroxy- or alkoxyureas 45 by reaction with substituted hydrazines or hydroxy- or alkoxylamines, respectively.

SCHEME 19



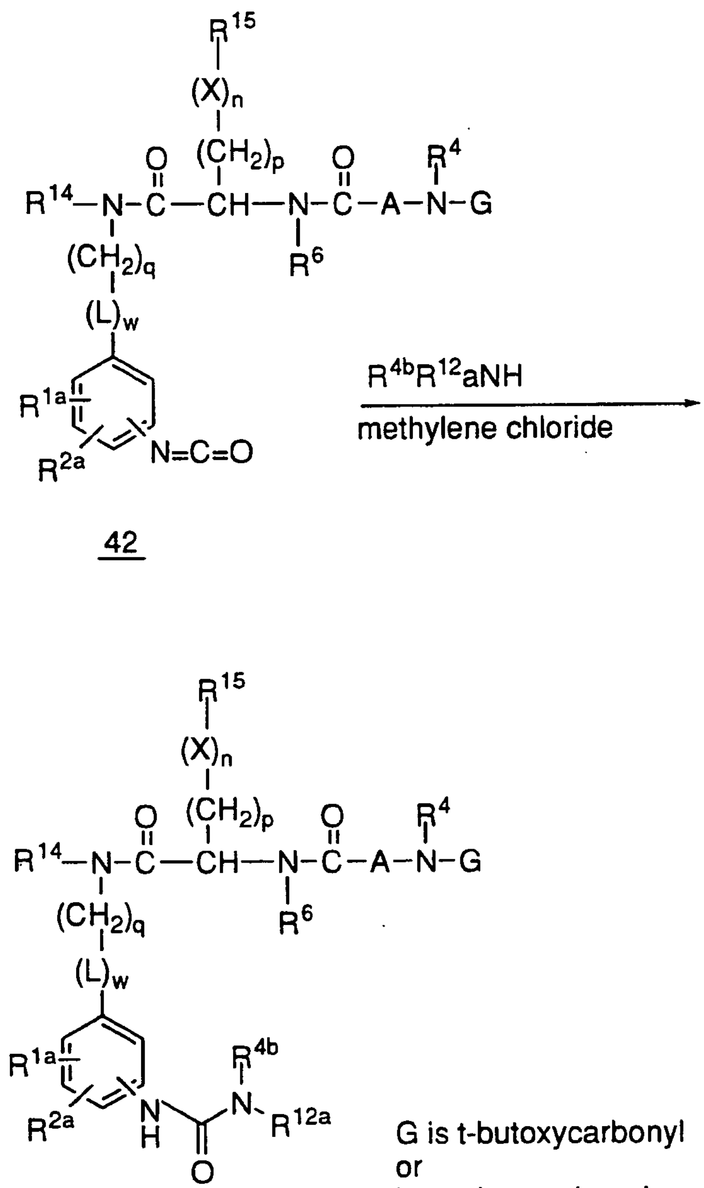
37



42

G is t-butoxycarbonyl
or
benzyloxycarbonyl

SCHEME 19 (cont'd)

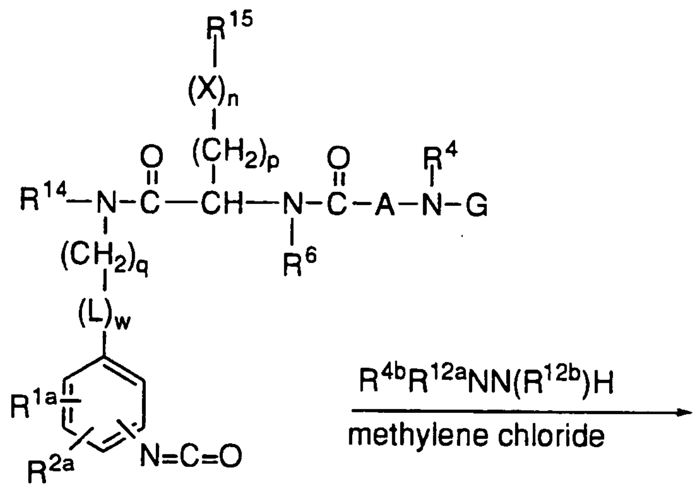


42

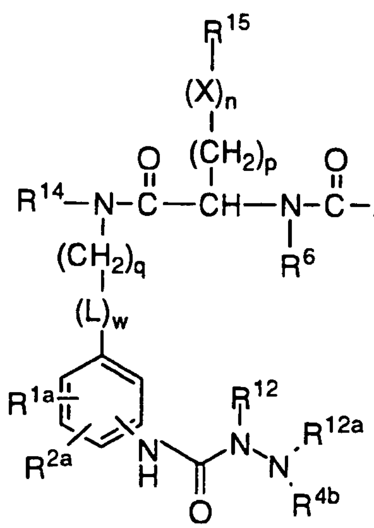
43

G is t-butoxycarbonyl or benzyloxycarbonyl

SCHEME 19 (cont'd)



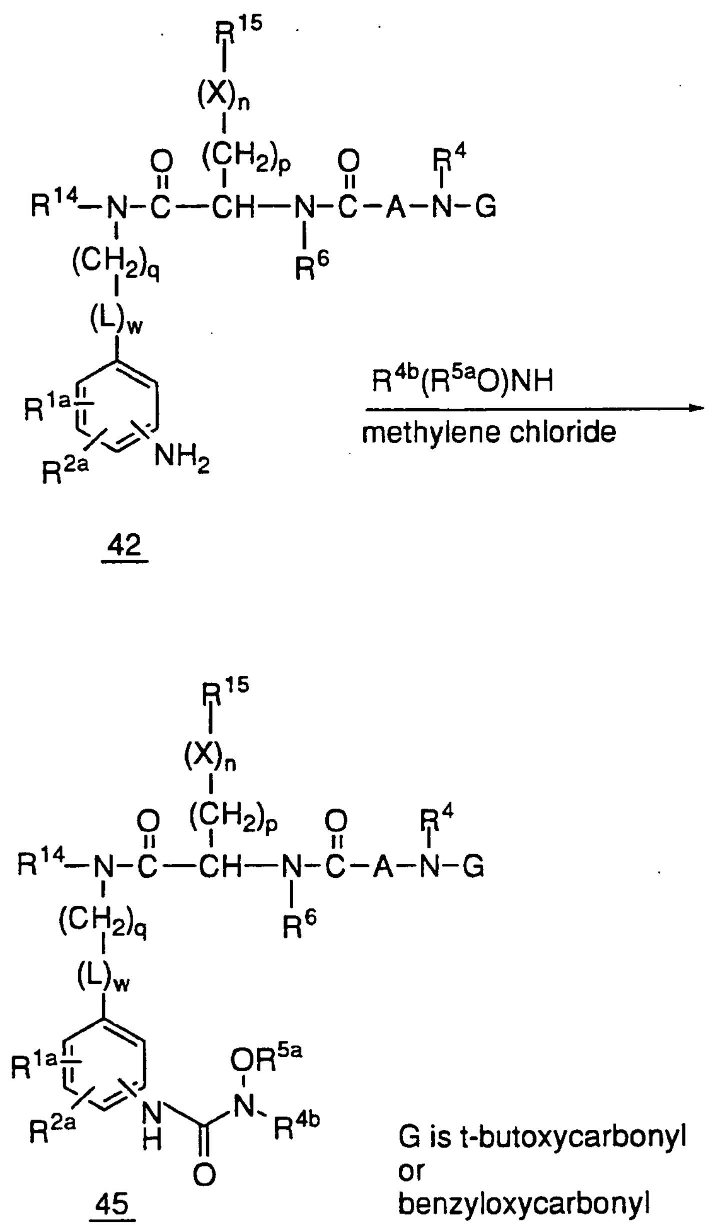
42



44

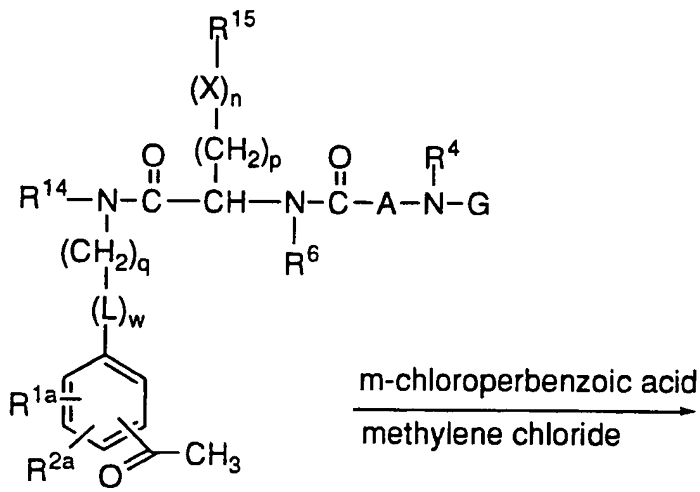
G is t-butoxycarbonyl
or
benzyloxycarbonyl

SCHEME 19 (cont'd)

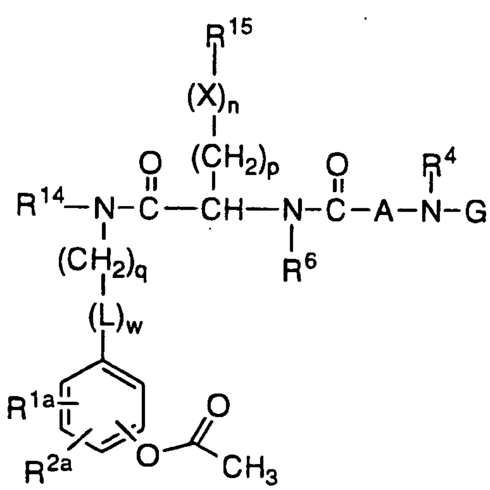


Compounds of formula I where R3a or R3b is a carbazate or carbamate derivative where attachment to the phenyl ring is through the oxygen atom of the carbazate or carbamate linkage are prepared from acetophenone intermediates 46 as indicated in Scheme 20.

SCHEME 20

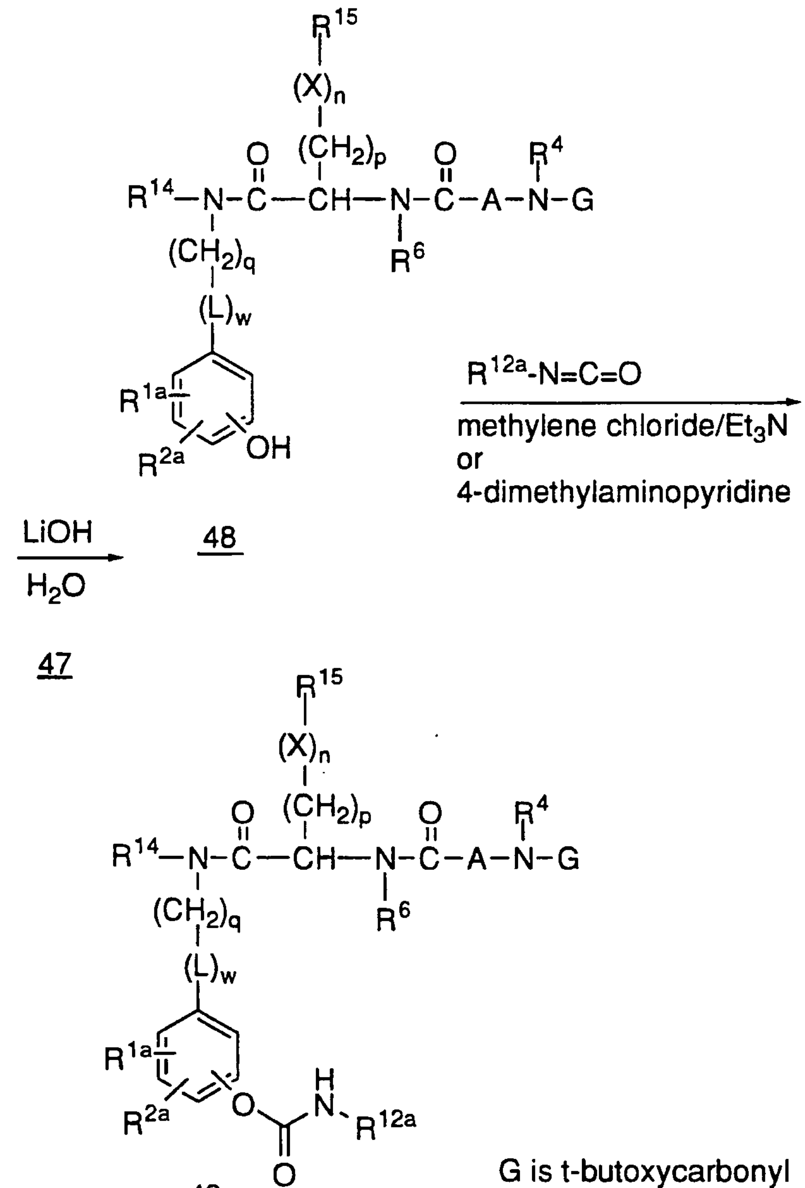


46



47

SCHEME 20 (cont'd)



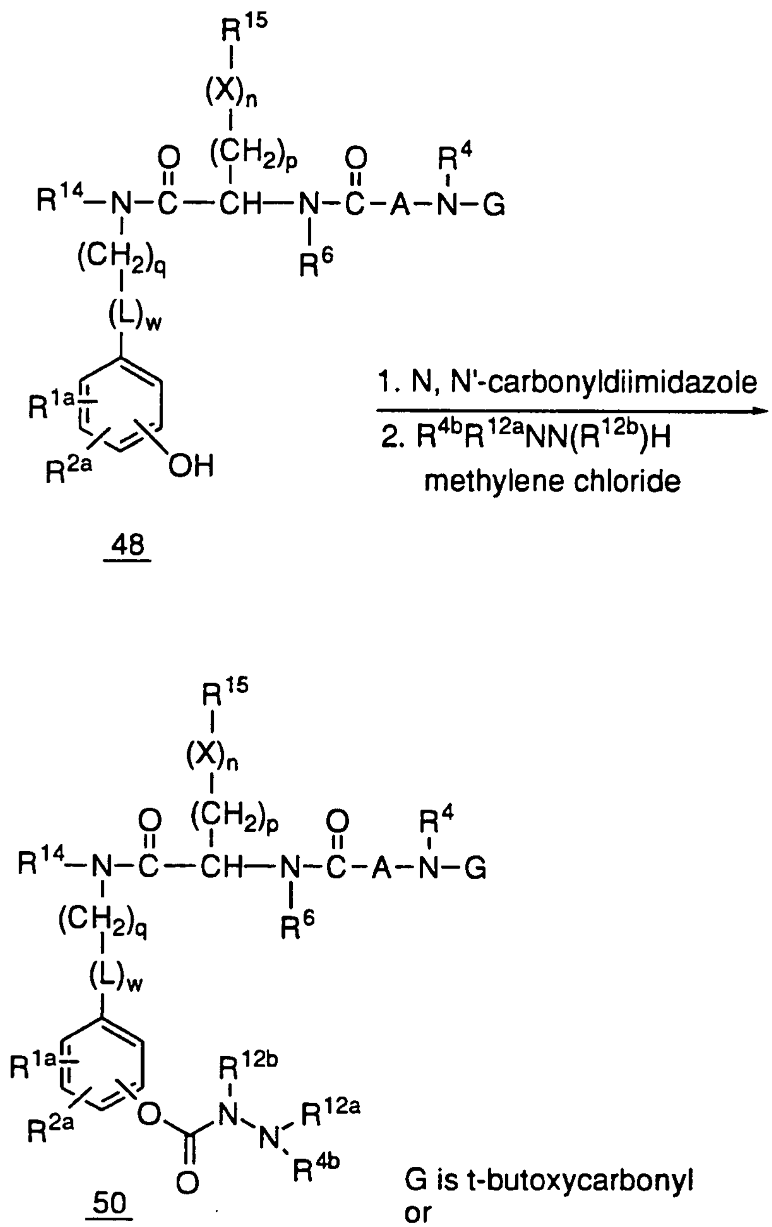
47

48

49

G is t-butoxycarbonyl
or
benzyloxycarbonyl

SCHEME 20 (cont'd)



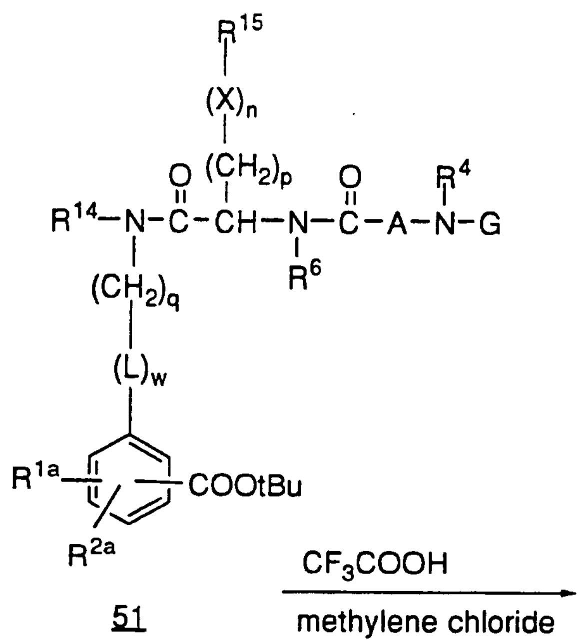
G is t-butoxycarbonyl or benzyloxycarbonyl

Oxidative rearrangement of 46 through the use of a peroxy-carboxylic acid (Baeyer-Villager reaction) such as m-chloroperbenzoic acid gives the ester 47 which is hydrolyzed in the presence of a strong base such as sodium or lithium hydroxide to give phenol 48.

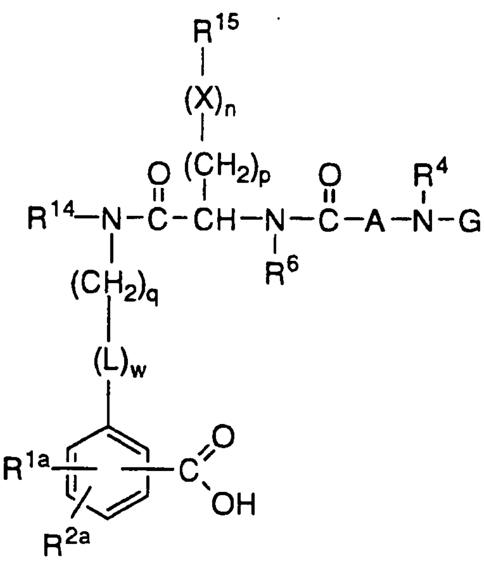
Reaction of 48 with an isocyanate leads directly to carbamate analogs 49. Additionally, treatment of 48 with N,N'-carbonyldiimidazole in dimethylformamide can form an activated intermediate which will react with substituted hydrazine reagents to give carbazate products 50.

Compounds of formula I wherein R^{3a} or R^{3b} contains the linkage -$CH_2N(R^{12b})$- can be prepared from the t-butyl ester intermediate 51 as described in Scheme 21. Removal of the t-butyl ester through the use of trifluoroacetic acid gives the carboxylic acid 24. It may be appreciated by one skilled in the art that the protecting group G in 51 must therefore be compatible with the strongly acidic conditions employed for ester cleavage, hence G is taken as benzyloxycarbonyl. Conversion of the carboxylic acid to the benzylamine derivative 52 can be achieved by a five-step sequence consisting of: 1) formation of a mixed anhydride with isobutyl chloroformate; 2) reduction with sodium borohydride to the benzyl alcohol; 3) formation of the mesylate with methanesulfonyl chloride; 4) formation of the azide by reaction with sodium azide, and finally, 5) reduction of the azide with tin(II) chloride. The benzylamine intermediate 52 can be further elaborated to 53 by the aforementioned reductive amination procedure.

SCHEME 21

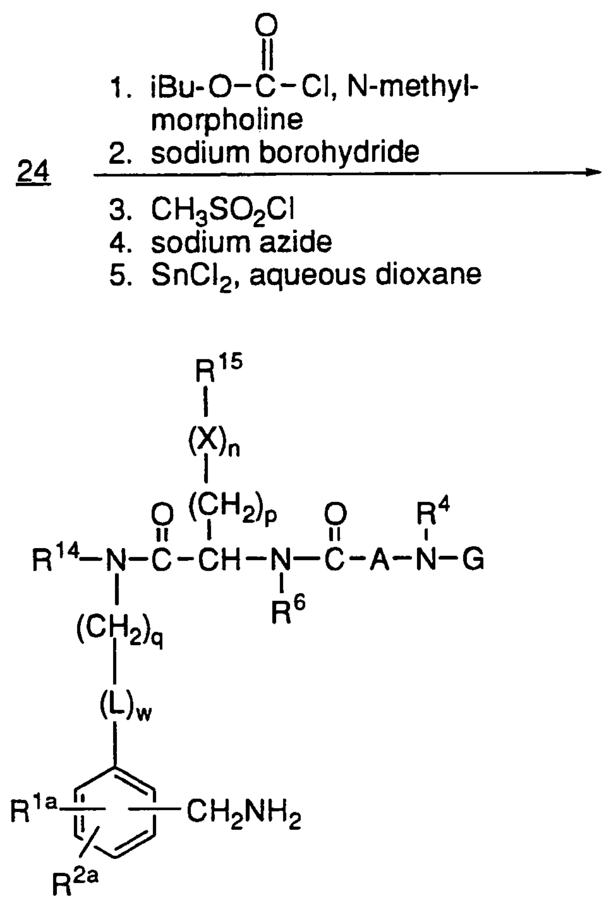


51



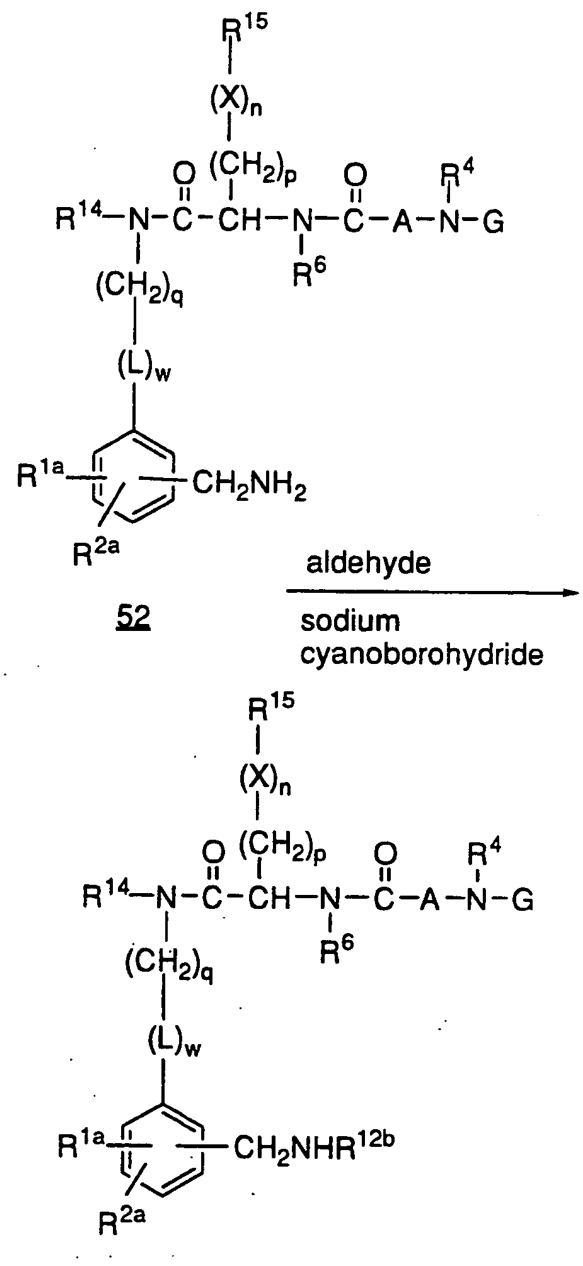
24 G is benzyloxycarbonyl

SCHEME 21 (Cont'd)



52 G is benzyloxycarbonyl

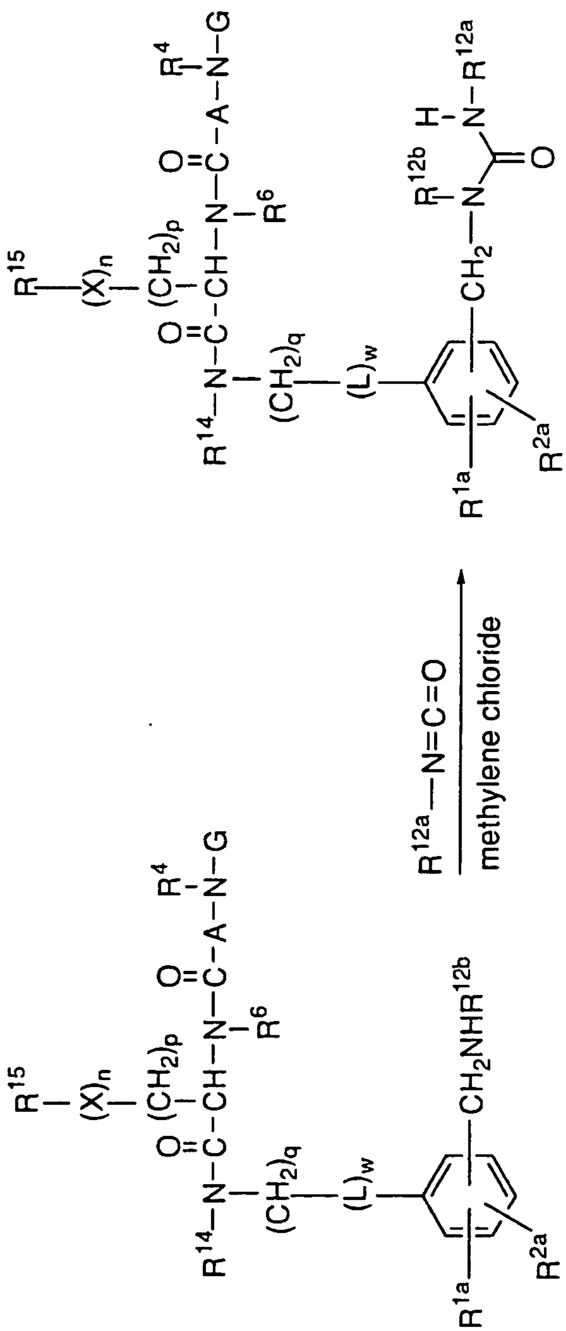
SCHEME 21 (Cont'd)



G is benzyloxycarbonyl

Reaction of amine 53 with the appropriate reagents to form urea-linked compounds 54 and 55 carbamate-linked compounds 56, and amide-linked structures 57 are illustrated in Scheme 22.

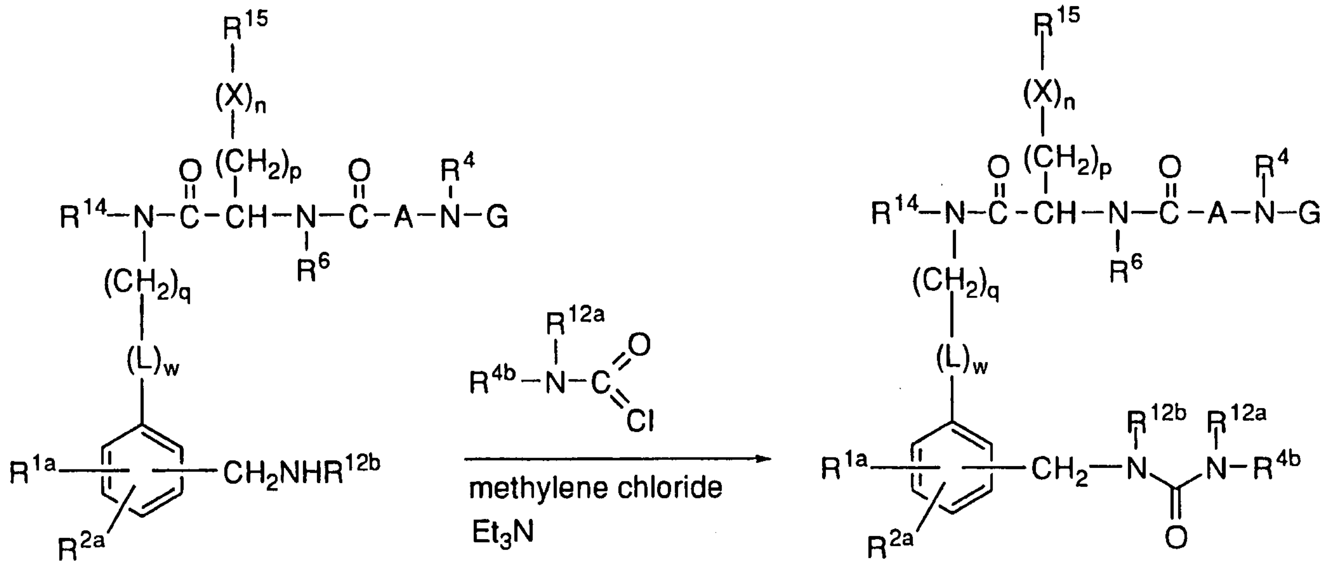
SCHEME 22



53

54

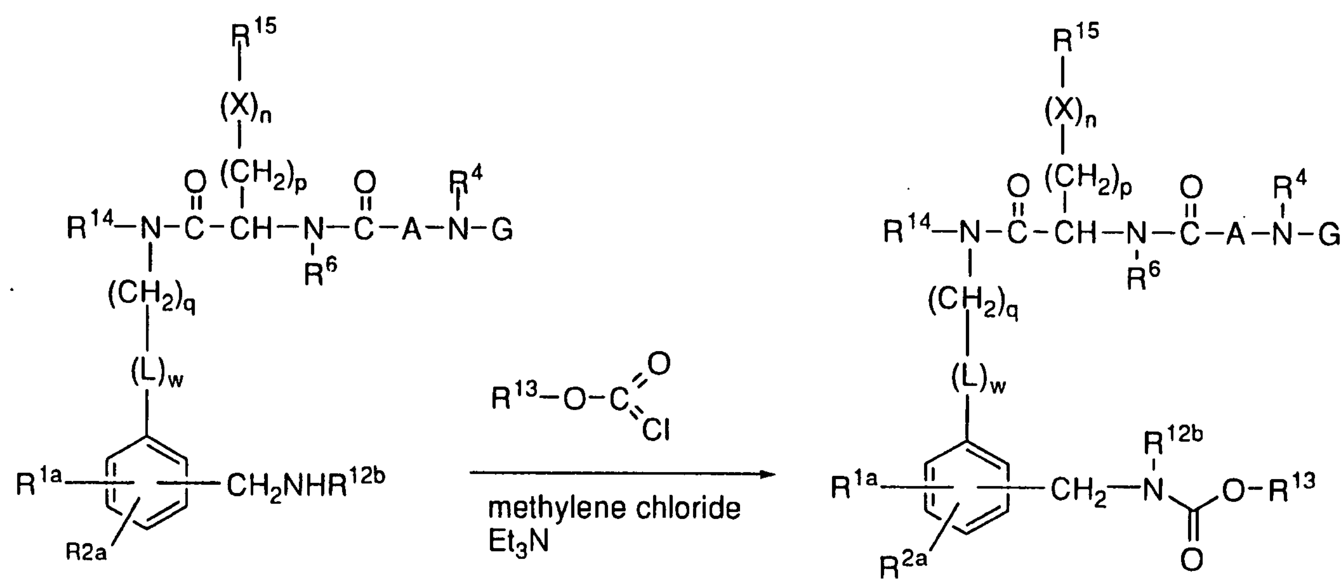
SCHEME 22 (CONT'D)



53

55

SCHEME 22 (CONT'D)

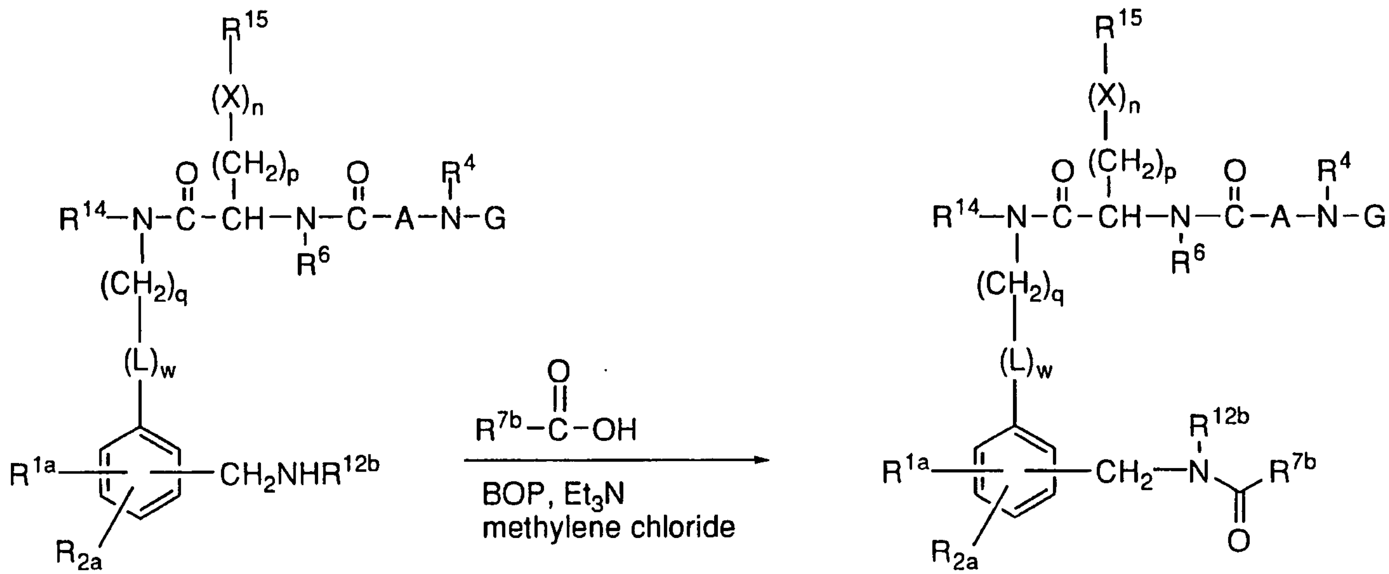


53

56

G is benzyloxycarbonyl

SCHEME 22 (CONT'D)

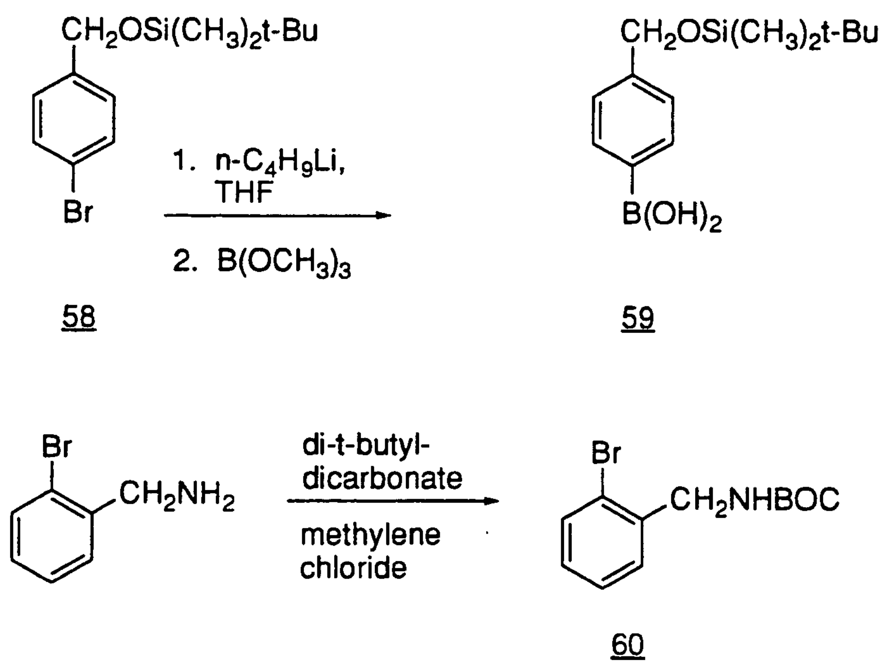


53 57

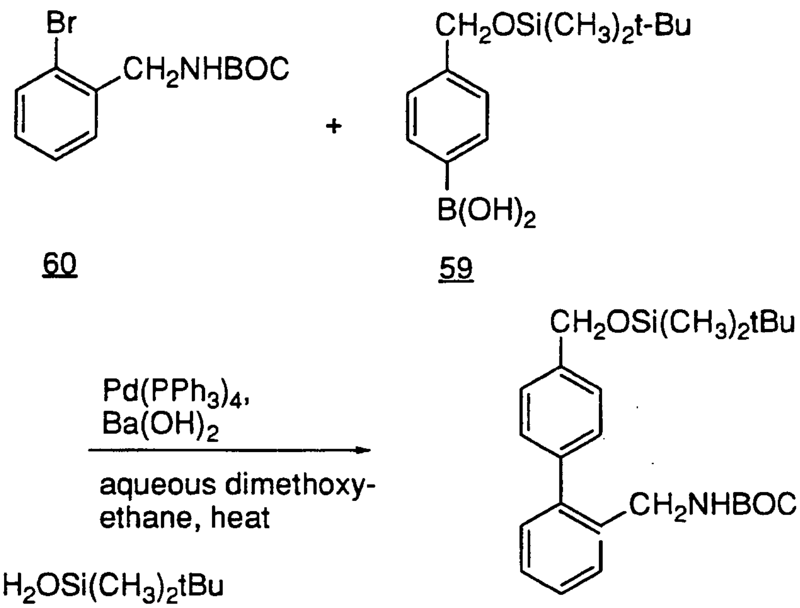
G is benzyloxycarbonyl

A useful preparation of the protected benzylamine intermediate 62 is shown in Scheme 23. Metallation of 4-bromobenzyl t-butyldimethylsilylether 58 with n-butyllithium followed by treatment with trimethyl borate gives the aryl boronic acid 59. Reaction of 59 with 2-bromo-N-(t-butoxycarbonyl)benzylamine 60 in the presence of tetrakis(triphenylphosphine)palladium(0) and barium hydroxide in aqueous 1,2-dimethoxyethane at elevated temperature gives the coupled product 61 in good yield. Desilylation is carried out by treatment with tetra-n-butylammonium fluoride; conversion to the O-methanesulfonate 62 is achieved by reaction of the intermediate benzyl alcohol with methanesulfonic anhydride. Conversion to the requisite amine derivative V is achieved by the procedure described in Scheme 5.

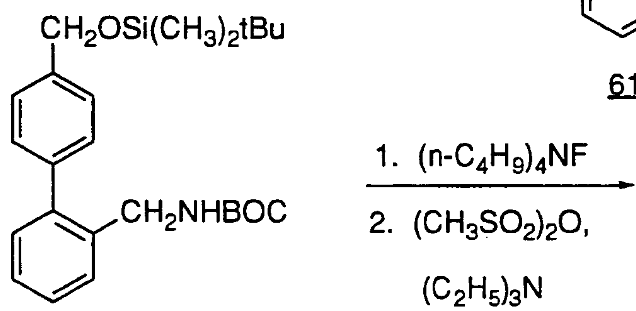
SCHEME 23



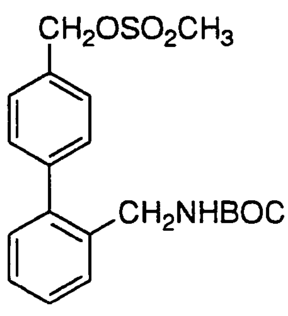
SCHEME 23 (Cont'd)



61



61

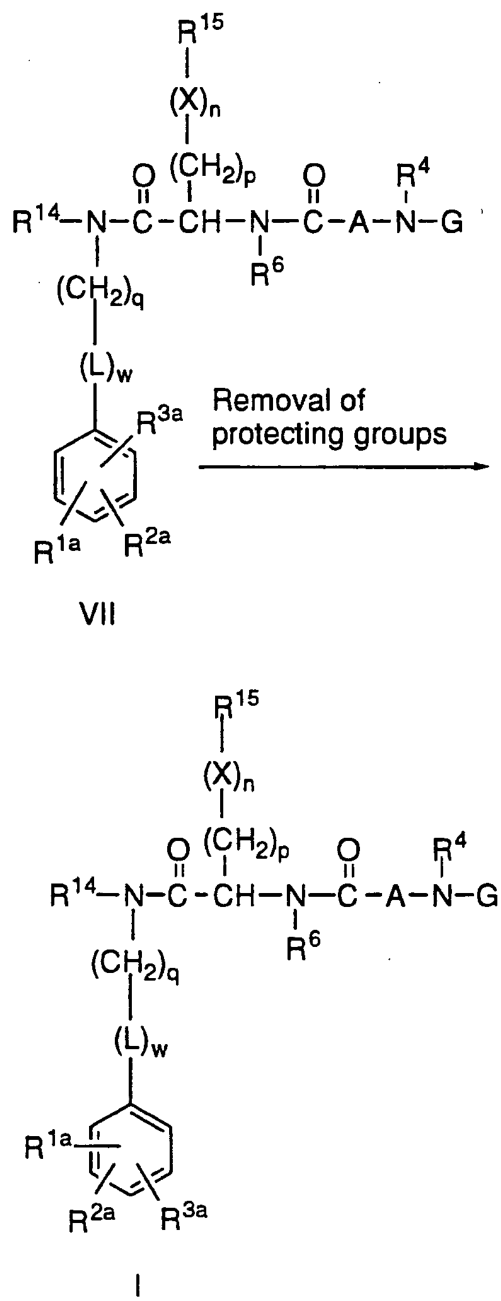


61

BOC is t-butoxycarbonyl

Conversion to the final products of formula I wherein R^5 is hydrogen, is carried out by simultaneous or sequential removal of all protecting groups from intermediate VII as illustrated in Scheme 24. Removal of benzyloxycarbonyl groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a platinum or palladium catalyst in a protic solvent such as methanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of benzyloxycarbonyl groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid. Catalytic hydrogenation is also employed in the removal of N-triphenylmethyl (trityl) protecting groups. Removal of t-butoxy-carbonyl (BOC) protecting groups is carried out by treatment of a solution in a solvent such as methylene chloride or methanol, with a strong acid, such as hydrochloric acid or trifluoroacetic acid. Conditions required to remove other protecting groups which may be present can be found in Protective Groups in Organic Synthesis.

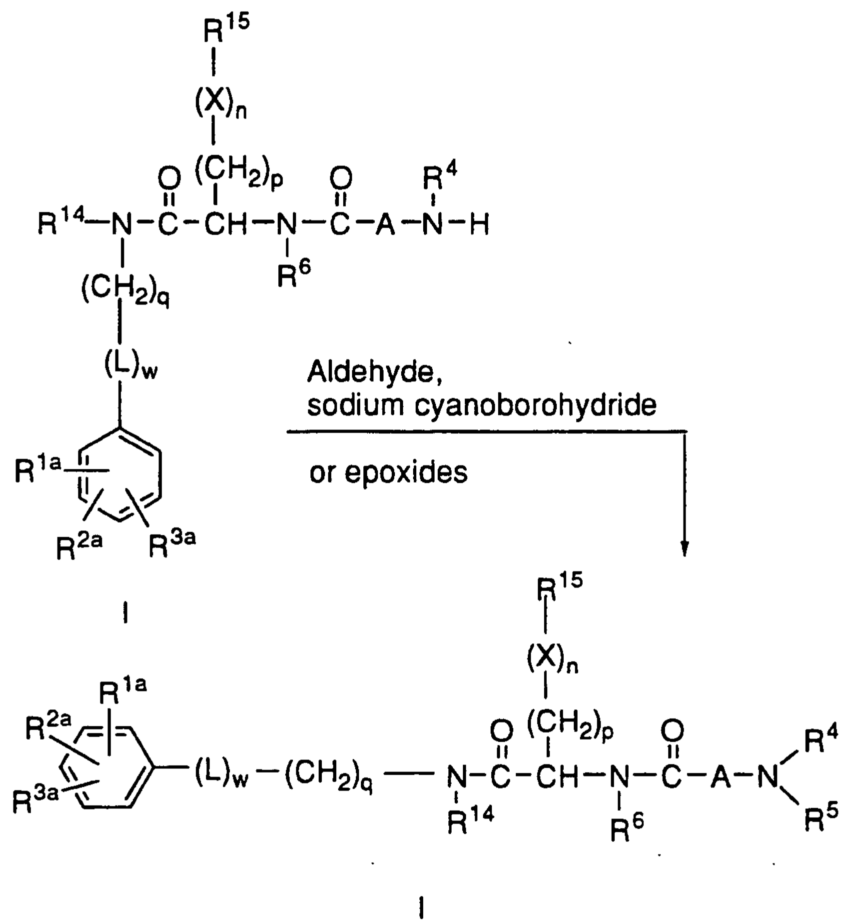
SCHEME 24



Compounds of formula I wherein R^4 and R^5 are each hydrogen can be further elaborated by reductive alkylation with an

aldehyde by the aforementioned procedures or by alkylations such as by reaction with various epoxides as shown in Scheme 25. The products, obtained as hydrochloride or trifluoroacetate salts, are conveniently purified by reverse phase high performance liquid chromatography (HPLC) or by recrystallization.

SCHEME 25



It is noted that the order of carrying out the foregoing reaction schemes is not significant and it is within the skill of one skilled in the art to vary the order of reactions to facilitate the reaction or to avoid unwanted reaction products.

The growth hormone releasing compounds of Formula I are useful in vitro as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, pinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive intestinal peptides, e.g., bombesin; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone in vivo. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, and to increase milk production in such animals. In addition, these compounds can be administered to humans in vivo as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered in vivo to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly

determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise a growth promoting agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic or other pharmaceutically active material.

Growth promoting agents include, but are not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the disclosed novel substituted dipeptide analogs is in combination with other growth hormone secretagogues such as GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890; and publications WO 89/07110 and WO 89/07111 and B-HT920 or growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2. A still further use of the disclosed novel substituted dipeptide analogs is in combination with $\alpha 2$ adrenergic agonists or $\beta 3$ adrenergic agonists in the treatment of obesity or in combination with parathyroid hormone or bisphosphonates, such as MK-217 (alendronate), in the treatment of osteoporosis.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: stimulating growth hormone release in elderly humans; Prevention of catabolic side effects of glucocorticoids, treatment of osteoporosis, stimulation of the immune

system, treatment of retardation, acceleration of wound healing, accelerating bone fracture repair, treatment of growth retardation, treating renal failure or insufficiency resulting in growth retardation, treatment of physiological short stature, including growth hormone deficient children, treating short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; Accelerating the recovery and reducing hospitalization of burn patients; Treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushings syndrome; Induction of pulsatile growth hormone release; Replacement of growth hormone in stressed patients; Treatment of osteochondrodysplasias, Noonans syndrome, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; Attenuation of protein catabolic response after a major operation; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS. Treatment of hyperinsulinemia including nesidioblastosis; Adjuvant treatment for ovulation induction; To stimulate thymic development and prevent the age-related decline of thymic function; Treatment of immunosuppressed patients; Improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; Stimulation of osteoblasts, bone remodelling, and cartilage growth; Stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; Growth promotant in livestock; and stimulation of wool growth in sheep.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage

forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The

selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzene-butanamide, trifluoroacetate

Step A: 5-Phenyltetrazole

Zinc chloride (3.3 g, 24.3 mmol, 0.5 eq) was added to 15 mL of N,N-dimethylformamide in small portions while maintaining the temperature below 60°C. The suspension of zinc chloride was cooled to room temperature and treated with 5.0 g of benzonitrile (48.5 mmol, 1.0 eq) followed by 3.2 g of sodium azide (48.5 mmol, 1.0 eq). The heterogeneous mixture was heated at 115°C with agitation for 18 hours. The mixture was cooled to room temperature, water (30 mL) was added and the mixture acidified by the addition of 5.1 mL of concentrated hydrochloric acid. The mixture was cooled to 0°C and aged for one hour, then filtered and the filter cake washed with 15 mL of cold 0.1N HCl then dried at 60°C under vacuum to afford 6.38 g (43.7 mmol, 90%) of the product.

Step B: 5-Phenyl-2-trityltetrazole

To a suspension of 5.0 g (34.2 mmol) of 5-phenyltetrazole in 55 mL of acetone was added 5.0 mL of triethylamine (3.6 g, 35.6 mmol, 1.04 eq). After 15 minutes, a solution of 10.0 g of triphenylmethyl chloride (35.9 mmol, 1.05 eq) in 20 mL of tetrahydrofuran was added and the mixture stirred at room temperature for one hour.

Water (75 mL) was slowly added and the mixture stirred for one hour at room temperature. The product was collected by filtration, washed with 75 mL of water and dried at 60°C under vacuum to give 13.3 g (34.2 mmol, 100%) of the product.

Step C: N-Triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)]tetrazole

A solution of zinc chloride (6.3 g, 46.2 mmol, 0.6 eq) in 35 mL of tetrahydrofuran was dried over molecular sieves. 5-Phenyl-2-trityltetrazole (30.0 g, 77.3 mmol, 1.0 eq) was dissolved in 300 mL of dry tetrahydrofuran and the solution gently stirred while being degassed three times by alternating vacuum and nitrogen purges. The stirred solution was cooled to -15°C and treated slowly with 50.5 mL of 1.6 M n-butyllithium in hexane (80.0 mmol, 1.05 eq) so as to maintain the temperature below -5°C. The solution was maintained at -5 to -15°C for 1.5 hours then treated with the dried zinc chloride solution and allowed to warm to room temperature.

In a separate flask, 4-iodotoluene (20.17 g, 92.5 mmol, 1.2 eq) and bis(triphenylphosphine)nickel(II)dichloride (1.5 g, 2.3 mmol, 0.03 eq) were dissolved in 60 mL of tetrahydrofuran, then degassed and left under an atmosphere of nitrogen. The mixture was cooled to 5°C and treated with 1.5 mL of 3.0 M solution of methylmagnesium chloride in tetrahydrofuran (4.5 mmol, 0.06 eq) so as to keep the temperature below 10°C. The solution was warmed to room temperature and added, under nitrogen purge, to the arylzinc solution. The reaction mixture was stirred vigorously for 8 hours at room temperature then quenched by the slow addition of a solution of 10 mL of glacial acetic acid (1.6 mmol, 0.02 eq) in 60 mL of tetrahydrofuran at a rate so that the temperature was maintained below 40°C. The mixture was stirred for 30 minutes and 150 mL of 80% saturated aqueous sodium chloride was added; the reaction mixture was extracted for 30 minutes and the layers allowed to separate. The organic layer was removed and washed with 150 mL of 80% saturated aqueous sodium chloride buffered to pH >10 by the addition of ammonium hydroxide. The organic phase was removed and concentrated under vacuum to

approximately 50 mL then 250 mL of acetonitrile was added. The mixture was again concentrated under vacuum to 50 mL and acetonitrile added to make the final volume 150 mL. The resulting slurry was cooled at 5°C for 1 hour then filtered and washed with 50 mL of cold acetonitrile followed by 150 mL of distilled water. The filter cake was air dried to a free flowing solid then further dried under vacuum at 50°C for 12 hours to afford 30.0 g (62.8 mmol, 81%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 2.28 (s,3H), 6.9-7.05 (m, 10H), 7.2-7.5 (m, 12H), 7.9 (m, 1H).

Step D: N-Triphenylmethyl-5-[2-(4'-bromomethylbiphen4-yl)]tetrazole

A solution of 3.15 g (6.6 mmol) of N-triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)]tetrazole in 25 mL of methylene chloride was treated with 1.29 g (7.25 mmol, 1.1 eq) of N-bromosuccinimide, 80 mg (0.5 mmol, 0.07 eq) of AIBN, 200 mg of sodium acetate and 200 mg of acetic acid. The mixture was heated at reflux for 16 hours then cooled and washed with saturated aqueous sodium bicarbonate. The organic layer was removed, dried over sodium sulfate, filtered and concentrated to a minimum volume by atmospheric distillation. Methyl t-butyl ether was added and distillation continued until almost all the methylene chloride was removed the the total volume reduced to approximately 12 mL and 12 mL of hexanes was then added. The mixture was kept at room temperature for 2 hours and the product isolated by filtration, washed with hexanes then dried under vacuum at 50°C to give 2.81 g (5.04 mmol, 76%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 4.38 (s, 2H), 6.9-8.0 (m, 23H). NMR indicates presence of approximately 1% of the starting material and 7% of the dibromo derivative.

Step E: N-Triphenylmethyl-5-[2-(4'-azidomethylbiphen-4-yl)]tetrazole

To 5.57 g (10 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)]tetrazole in 20 mL of dimethyl sulfoxide was added 614 mg (12.5 mmol, 1.25 eq) of pulverized lithium azide. The

reaction was stirred at room temperature for 4 hours, during which time a thick precipitate formed. The precipitated solids were collected by filtration and washed with methanol, water, and then methanol again, and dried under vacuum for 16 hours to yield 4.06 g (78%) of the product as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): 3.46 (s, 2H), 6.82-7.55 (m, 22H), 7.95 (m, 1H).

<u>Step F</u>: <u>N-Triphenylmethyl-5-[2-(4'-aminomethylbiphen-4-yl)]tetrazole</u>

To a solution of 4.06 g (7.8 mmol) of <u>N</u>-triphenylmethyl-5-[2-(4'azidomethylbiphen-4-yl)]-tetrazole in 15 mL of tetrahydrofuran was added 2.05 g (7.8 mmol, l eq) of triphenylphosphine in small portions. The mixture was stirred at room temperature for 2 hours, at which time 0.2 mL of water was added and the reaction mixture stirred for 16 hours. The reaction mixture was concentrated to dryness under vacuum and the crude product chromatographed on a silica flash column, eluting with chloroform, to give 1.5 g (3.03 mmol, 39%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 2.21 (br s, 2H), 3.75 (s, 2H), 6.80-7.94 (m, 22H), 7.94 (m, 1H).

<u>Step G</u>: <u>(R)-α-[t-Butoxycarbonylamino]-N-[[2'-(N-triphenyl-methyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzene-butanamide</u>

To a solution of 30.5 mg (0.11 mmol) of <u>N</u>-BOC-<u>D</u>-homophenylalanine in 1 mL of methylene chloride at room temperature under a nitrogen atmosphere was added 54 mg (0.11 mmol, l eq) of <u>N</u>-triphenylmethyl-5-[2-(4'aminomethylbiphen-4-yl)]tetrazole (Step F), 25 mg (0.13 mmol, 1.2 eq) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 13 mg (0.13 mmol, 1.2 eq) of triethylamine. The reaction was stirred at room temperature for 16 hours, then transferred to a separatory funnel and washed with 2 mL of 5% aqueous citric acid and 2 mL of saturated aqueous sodium bicarbonate. The organic layer was removed, dried over magnesium sulfate, filtered and evaporated to dryness under vacuum. The residue was chromato-

graphed on a silica flash column, eluting with hexane/ethyl acetate (5:1), to give 29 mg (35%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.43 (s, 9H), 2.05 (m, 2H), 2.67 (t, 8Hz, 2H), 4.05 (m, 1H), 4.32 (m, 1H), 4.99 (m, 1H), 6.19 (m, 1H), 6.78-7.15 (m, 27H), 7.95 (m, 1H).

<u>Step H</u>: <u>(R)-α-[t-Butoxycarbonylamino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide</u>

A solution of 29 mg (0.038 mmol) of the intermediate obtained in Step G in 1 mL of methanol was hydrogenated at room temperature and one atmosphere over 4 mg of 20% palladium hydroxide on carbon for two hours. The reaction mixture was then filtered through Celite to remove the catalyst, the solvent removed under vacuum and the residue flash chromatographed on silica to yield 19 mg (95%) of the title compound. ^{1}H NMR (200 MHz, CD_3OD): 1.43 (s, 9H), 1.95 (m, 2H), 2.64 (m, 2H), 4.00 (m, 1H), 4.34 (t, 5Hz, 2H), 7.00-7.30 (m, 8H), 7.50 (m, 5H). FAB-MS: calculated for $C_{29}H_{32}N_6O_3$ 512; found 513 (M+1, 24%).

<u>Step I</u>: <u>(R)-α-Amino-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4yl]methyl]-benzenebutanamide, hydrochloride</u>

A solution of 19 mg (0.037 mmol) of the intermediate obtained in Step H in 1 mL of methanol was treated with one drop of concentrated hydrochloric acid. The mixture was stirred at room temperature for 16 hours then evaporated to dryness under vacuum. The crude product was purified on reverse phase HPLC on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid [linear gradient: 60% methanol to 80% methanol over 10 minutes], to yield 14 mg (84%) of the product. ^{1}H NMR (200 MHz, CD_3OD): 2.11 (m, 2H), 2.64 (m, 2H), 3.89 (t, 6Hz, 1H), 4.42 (s, 2H), 7.05-7.32 (m, 8H), 7.58 (m, 5H). FAB-MS: calculated for $C_{24}H_{24}N_6O$ 412; found 413 (M+1,100%).

<u>Step J</u>: <u>2,2-Dimethylbutanedioic acid, 4-methyl ester</u>

2,2-Dimethylsuccinic acid (20 g, 137 mmol) dissolved in 200 mL of absolute methanol at 0°C was treated dropwise with 2 mL of

concentrated sulfuric acid. After the addition was complete, the mixture was allowed to warm to room temperature and stir for 16 hours. The mixture was concentrated under vacuum to 50 mL and slowly treated with 200 mL of saturated aqueous sodium bicarbonate. The mixture was washed with hexane (3x) and the aqueous layer removed and cooled in an ice bath. The mixture was acidified to pH 2 by slow addition of 6<u>N</u> HCl then extracted with ether (8x). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was dried at room temperature under vacuum to afford 14.7 g (91.8 mmol, 67%) of the product as a viscous oil that slowly solidified upon standing. ^{1}H NMR (200 MHz, $CDCl_3$): 1.29 (s, 6H), 2.60 (s, 2H), 3.65 (s, 3H).

Step K: 3-Benzyloxycarbonylamino-3-methylbutanoic acid, methyl ester

To 14.7 g (91.8 mmol) of 2,2-dimethylbutanedioic acid-4-methyl ester in 150 mL of benzene was added 13 mL of triethylamine (9.4 g, 93 mmol) followed by 21.8 mL of diphenylphosphoryl azide (27.8 g, 101 mmol). The mixture was heated under nitrogen at reflux for 45 minutes then 19 mL (19.9 g, 184 mmol) of benzyl alcohol was added and refluxing continued for 16 hours. The mixture was cooled, filtered and the filtrate concentrated to a minimum volume under vacuum. The residue was redissolved in 250 mL of ethyl acetate, washed with water, saturated aqueous sodium bicarbonate (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and the filtrate concentrated to a minimum volume under vacuum. The crude product was purified by medium pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (4:1), to afford 18.27 g (68.9 mmol, 75%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.40 (s, 6H), 2.69 (s, 2H), 3.63 (s, 3H), 5.05 (s, 2H), 5.22 (br s, 1H), 7.32 (s, 5H).

Step L: 3-Benzyloxycarbonylamino-3-methylbutanoic acid

A solution of 18.27 g (68.9 mmol) of 3-benzyloxycarbonylamino-3-methylbutanoic acid methyl ester in 20 mL of methanol at room temperature was treated dropwise with 51 mL of 2N NaOH (102 mmol). The mixture was stirred at room temperature for 16 hours then transferred to a separatory funnel and washed with hexane (3x). The aqueous layer was removed, cooled to 0°C and slowly acidified to pH 2 (paper) by dropwise addition of 6N HCl. This mixture was extracted with ether (6x); combined extracts were washed with 1N HCl and brine, then dried over magnesium sulfate, filtered and solvent removed under vacuum to afford 17.26 g (68.7 mmol, 99%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.42 (s, 6H), 2.77 (s, 2H), 5.06 (s, 2H), 5.2 (br s, 1H), 7.3 (s, 5H).

Step M: 3-Benzyloxycarbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester

A solution of 2.93 g (11.7 mmol, 0.85 eq) of 3-benzyloxycarbonylamino-3-methylbutanoic acid in 5 mL of methylene chloride at room temperature was treated with 1.61 g (14.0 mmol) of N-hydroxysuccinimide followed by 2.67 g (14.0 mmol, 1 eq) of 1(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction mixture was stirred for 16 hours then transferred to a separatory funnel, washed with water and dilute aqueous sodium bicarbonate. The organic layer was removed, dried over magnesium sulfate, filtered, and solvents removed under vacuum. The crude product was chromatographed on a silica flash column, eluting with hexane/ethyl acetate (1:1), to give 3.9 g (quantitative) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.51 (s, 6H), 2.80 (s, 4H), 3.12 (s, 2H), 5.13 (s, 2H), 7.37 (s, 5H). FAB-MS: calculated for $C_{17}H_{20}N_2O_6$ 348; found 349 (M+1, 40%).

Step N: (R)-α-[(3-Benzyloxycarbonylamino-3-methyl-1-oxo-butyl)amino]-N-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4yl]methyl]benzenebutanamide

A solution of 12 mg (0.023 mmol) of the intermediate obtained in Step I in 0.5 mL of methylene chloride at room temperature was treated with 9.2 mg (0.027 mmol, 1.2 eq) of 3-benzyloxy-carbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester (Step M) and 3.5 mg (0.027 mmol, 1.2 eq) of diisopropylethylamine. The reaction mixture was stirred at room temperature for 48 hours. Solvents were emoved under vacuum and the crude residue was purified on HPLC to give 14 mg of product. ^{1}H NMR (200 MHz, CD_3OD): 1.29 (s, 3H), 1.36 (s, 3H), 1.90 (m, 3H), 2.45 (m, 3H), 4.31 (m, 1H), 4.72 (d, 20Hz, 1H), 5.02 (d, 20Hz, 1H), 7.00-7.62 (m, 18H). FAB-MS: calculated for $C_{37}H_{39}N_7O_4$ 645; found 646 (M+1, 100%).

Step O: (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide, tri-fluoroacetate

A solution of 14 mg (0.21 mmol) of the intermediate obtained in Step N in 1 mL of methanol was hydrogenated at room temperature and one atmosphere over 1 mg of 20% palladium hydroxide on carbon for 16 hours. The reaction mixture was filtered through Celite and the filtrate concentrated under vacuum and the residue chromatographed on reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient; 65% methanol increased to 85% over 10 minutes), to give 10 mg (72%) of the title compound. ^{1}H NMR (200 MHz, CD_3OD): 1.32 (s, 3H), 1.36 (s, 3H), 1.81 (m, 1H), 1.95 (m, 2H), 2.26 (m, 1H), 2.52 (s, 1H), 2.63 (m, 1H), 4.34 (m, 1H), 4.76 (d, 14Hz, 1H), 4.95 (d, 14Hz, 1H), 7.01-7.70 (m, 13H). FAB-MS: calculated for $C_{29}H_{33}N_7O_2$ 511; found 512 (M+1, 100%).

EXAMPLE 2

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzene-propanamide, trifluoroacetate

The title compound was prepared from N-BOC-D-phenylalanine by the methods described in Example 1. ^{1}H NMR (200 MHz, $CDCl_3$): 1.27 (s, 3H), 1.40 (s, 3H), 2.49 (d, 15Hz, 1H), 2.62 (d, 15Hz, 1H), 3.10 (m, 2H), 4.44 (m, 2H), 4.80 (m, 1H), 7.16 (s, 4H), 7.35 (s, 5H); 7.70 (m, 4H). FAB-MS: calculated for $C_{28}H_{31}N_7O_2$ 497; found 498 (M+1,100%).

EXAMPLE 3

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide, trifluoroacetate

Step A: (R)-α-[t-Butoxycarbonylamino]-N-[[2'-(N-triphenyl-methyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-(N_{im}-formyl)indole-3-propanamide

Prepared from N-triphenylmethyl-5-[2-(4'-aminomethyl-biphen-4-yl)]tetrazole and N_{im}-formyl-N_α-BOC-D-tryptophan by the procedure described in Example 1, Step G. ^{1}H NMR (200 MHz, $CDCl_3$): 1.40 (s, 9H), 3.18 (br s, 2H), 4.24 (br s, 2H), 4.48 (m, 1H), 5.24 (s, 1H), 6.28 (s, 1H), 6.70-7.70 (m, 27H), 7.90 (m, 1H), 8.82 (br s, 1H).

Step B: (R)-a-[t-Butoxycarbonylamino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-(N_{im}-formyl)indole-3-propanamide

Prepared from the intermediate obtained in Step A by the procedure described in Example 1, Step H. ^{1}H NMR (200 MHz, CD_3OD): 1.38 (s, 9H), 3.14 (m, 3H), 6.90-7.70 (m, 13H), 9.02 (br s, 1H). FAB-MS: calculated for $C_{30}H_{31}N_7O_4$ 553; found 554 (M+1,40%).

Step C: (R)-α-Amino-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyll-4-yl]methyl]-(N_{im}-formyl)indole-3-propanamide, trifluoroacetate

A solution of 80 mg (0.14 mmol) of the intermediate obtained in Step B in 4 mL methylene chloride was treated with 1 mL of anisole followed by 4 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 1 hour, then all volatiles were removed under vacuum. The residue was purified by reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (45:55), to give 64 mg (77%) of the product. ^1H NMR (200 MHz, CD_3OD): 3.26 (m, 2H), 4.11 (t, 6Hz, 1H), 4.28 (m, 2H), 6.99 (s, 4H), 7.28-7.70 (m, 9H), 8.75 (br s, 1H). FAB-MS: calculated for $C_{26}H_{23}N_7O_2$ 465; found 466 (M+1, 22%).

Step D: 4,4-Dimethylazetidin-2-one

A 3-neck 3L round bottom flask equipped with a magnetic stirrer, thermometer, cold finger condenser and nitrogen bubbler was charged with 1L of ether. The flask was cooled to -65°C and into it was condensed 500-600 mL of isobutylene. The cold finger condenser was replaced with a dropping funnel and 200 mL (325 g, 2.30 mol) of chlorosulfonyl isocyanate was added dropwise over 1.5 hours. The mixture was maintained at -65°C for 1.5 hours then the dry ice/acetone cooling bath replaced with methanol/ice and the internal temperature slowly increased to -5°C at which time the reaction initiated and the internal temperature rose to 15°C with evolution of gas. The internal temperature remained at 15°C for several minutes then dropped back down to -5°C and the mixture stirred at -5°C for 1 hour. The methanol/ice bath was removed and the reaction mixture warmed to room temperature and stirred overnight.

The reaction mixture was transferred to a 3-neck 12L round bottom flask fitted with a mechanical stirrer and diluted with 2L of ether. The well-stirred reaction mixture was treated with 2L of saturated aqueous sodium sulfite. After 1 hour, an additional 1L of

saturated aqueous sodium sulfite was added followed by sufficient sodium bicarbonate to adjust the pH to approximately 7. The mixture was stirred another 30 minutes then the layers allowed to separate. The ether layer was removed and the aqueous layer reextracted with 2 x 1L of ether. The combined ether extracts were washed once with 500 mL of saturated aqueous sodium bicarbonate and once with 500 mL of saturated aqueous sodium chloride. The ether layer was removed, dried over magnesium sulfate, filtered and concentrated under vacuum to give 33 g of a pale yellow oil. The aqueous layer was made basic by the addition of solid sodium bicarbonate and extracted with 3 x 1L of ether. The combined ether extracts were washed and dried as described above, then combined with the original 33 g of pale yellow oil and concentrated under vacuum to give 67.7 g of product. Further extraction of the aqueous layer with 4 x 1L of methylene chloride and washing and drying as before gave an additional 74.1 g of product. Still further extraction of the aqueous layer with 4 x 1L of methylene chloride gave an additional 21.9 g of product. The combined product (163.7 g, 1.65 mol, 72%) was used in Step E without purification. ^1H NMR (200 MHz, $CDCl_3$): 1.45 (s, 6H), 2.75 (d, 3Hz, 2H), 5.9 (br s, 1H).

Step E: N-(t-Butoxycarbonyl)-4,4-dimethylazetidin-2-one

A 5L, 3-neck round bottom flask equipped with a magnetic stirrer, thermometer, nitrogen bubbler and addition funnel was charged with 88.2 g (0.89 mol) of 4,4-dimethylazetidin-2-one, 800 mL of methylene chloride, 150 mL of triethylamine (1.08 mol) and 10.9 g (0.089 mol) of 4-dimethylaminopyridine. To the stirred solution at room temperature was added dropwise over 15 minutes a solution of 235 g (1.077 mol) of di-t-butyl-dicarbonate in 300 mL of methylene chloride. The reaction mixture was stirred at room temperature overnight then diluted with 1L of methylene chloride and washed with 500 mL of saturated aqueous ammonium chloride, 500 mL of water, and 500 mL of saturated aqueous sodium chloride. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated

under vacuum to afford 180.3 g of crude product as an orange solid. The material was used directly in Step F without purification.
^1H NMR (200 MHz, $CDCl_3$): 1.50 (s, 9H), 1.54 (s, 6H), 2.77 (s, 2H).

Step F: 3-t-Butoxycarbonylamino-3-methylbutanoic acid

A 3L, 3-neck round bottom flask equipped with a magnetic stirrer, thermometer, nitrogen bubbler and addition funnel was charged with 180.3 g (0.89 mol) of N-(t-butoxycarbonyl)-4,4-dimethylazetidin-2-one dissolved in 1L of tetrahydrofuran. The solution was cooled to 0-5°C and treated dropwise with 890 mL of 1.0M aqueous lithium hydroxide over 30 minutes. The reaction mixture was stirred at 0-5°C for 2 hours then diluted with 1L of ether and 1L of water. The layers were allowed to separate and the aqueous layer was reextracted with an additional 1L of ether. The aqueous layer was acidified by the addition of 1L of saturated aqueous sodium bisulfate, then extracted with 1 x 1L and 2 x 500 mL of ether. The combined organic layer and ether extracts were washed with 500 mL of saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated under vacuum to give 173 g of a yellow oil that solidified upon standing. The material was slurried with warm hexane then filtered and dried under high vacuum to afford 168.5 g (0.775 mol, 87%) of product as a white solid.
^1H NMR (200 MHz, $CDCl_3$): 1.39 (s, 6H), 1.44 (s, 9H), 2.72 (s, 2H).
FAB-MS: calculated for $C_{10}H_{19}NO_4$ 217; found 218 (M+H, 54%).

Step G: (R)-α-[(3-t-Butoxycarbonylamino-3-methyl-1-oxo-butyl)amino]-N-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-(N_{im}-formyl)-indole-3-propanamide

A solution of 64 mg (0.11 mmol) of the intermediate obtained in Step C in 1 mL of methylene chloride at 0°C was treated with 25 mg (0.12 mmol, 1.1 eq) of dicyclohexylcarbodiimide and the resulting solution stirred at 0°C for 30 minutes. A solution of 53 mg (0.24 mmol, 2 eq) of 3-t-butoxycarbonylamino-3-methylbutanoic acid and 12 mg (0.12 mmol, 0.017 mL, 1.1 eq) of triethylamine in 1 mL of methylene chloride was added and the mixture stirred for 5 hours at

room temperature. The reaction mixture was evaporated to dryness under vacuum and the residue was dissolved in 1 mL of anisole and treated with 4 mL of trifluoroacetic acid. The mixture was stirred at room temperature for 30 minutes the concentrated under vacuum. The residue was taken up in methanol and the solids removed by filtration. The filtrate was concentrated under vacuum; the residue was purified by reverse phase high pressure liquid chromatography on C18 to yield 31 mg (42%) of the product. ^{1}H NMR (200 MHz, CD_3OD): 1.14 (s, 3H), 1.25 (s, 3H), 2.37 (d, 15Hz, 1H), 2,48 (d, 15Hz, 1H), 3.11 (m, 2H), 4.26 (m, 2H), 4.72 (m, 1H), 6.92-7.70 (m, 13H), 8.55 (br s, 1H). FAB-MS: calculated for $C_{31}H_{32}N_8O_3$ 564; found 565 (M+1, 80%).

Step H: (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide, trifluoroacetate

A solution of 31 mg (0.046 mmol) of the intermediate obtained in Step G in 1 mL of methanol was treated with 0.2 mL of concentrated hydrochloric acid and the resulting mixture heated at 65°C for 1.5 hours. All volatiles were removed under vacuum and the residue purified by reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (50:50), to give 20 mg (67%) of the title compound. ^{1}H NMR (200 MHz, CD_3OD): 1.15 (s, 3H), 1.28 (s, 3H), 2.38 (d, 16Hz, 1H), 2.50 (d, 16Hz, 1H), 3.19 (m, 2H), 4.20 (d, 14Hz, 1H), 4.32 (d, 14Hz, 1H), 4.73 (t, 7Hz, 1H), 6.90-7.70 (m, 13H). FAB-MS: calculated for $C_{30}H_{32}N_8O_2$ 536; found 536 (70%).

EXAMPLE 4

(R)-2-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-butanamide, trifluoroacetate

Step A: (R)-2-(t-Butoxycarbonylamino)-N-phenyl-butanamide

Prepared from N-BOC-D-2-aminobutanoic acid and aniline by the method described in Example 1, Step G. ^{1}H NMR (200 MHz, $CDCl_3$): 1.00 (t, 6Hz, 3H), 1.45 (s, 9H), 1.82 (m, 2H), 4.30 (m, 1H), 5.59 (d, 7Hz, 1H), 7.00-7.62 (m, 5H), 8.90 (br s, 1H). FAB-MS: calculated for $C_{15}H_{22}N_2O_3$ 278; found 279 (M+1, 40%).

Step B: (R)-2-(t-Butoxycarbonylamino)-N-phenyl-N-[[2'-(N-triphenylmethyl-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-butanamide

A solution of 70 mg (0.25 mmol) of (R)-2-(t-butoxycarbonylamino)-N-phenyl-butanamide in 0.5 mL of dry dimethylformamide was treated with 10 mg (0.25 mmol, 1 eq) of 60% sodium hydride oil dispersion. The mixture was stirred at room temperature for 20 minutes, then treated with a solution of 140 mg (0.25 mmol, 1 eq) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)]tetrazole (Example 1, Step D) in 0.5 mL of dry dimethylformamide. The mixture was stirred at room temperature for 2 hours, then quenched by the addition of 2 mL of water. The mixture was extracted several times with ethyl acetate; the combined extracts were washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate then dried over magnesium sulfate, filtered and the filtrate dried under vacuum. The crude material was chromatographed on a flash silica column, eluting with hexane/ethyl acetate (1:1), to give 91 mg (48%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 0.74 (t, 6Hz, 3H), 1.32 (s, 9H), 1.58 (m, 2H), 4.20 (m, 1H), 4.79 (s, 2H), 6.82-7.60 (m, 27H), 7.86 (m, 1H).

Step C: (R)-2-(t-Butoxycarbonylamino)-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]butanamide

Prepared from the intermediate obtained in Step B by the procedure described in Example 1, Step H. ^{1}H NMR (200 MHz, $CDCl_3$): 0.74 (t, 6Hz, 3H), 1.36 (s, 9H), 1.55 (m, 2H), 4.13 (m, 1H), 4.70 (d, 14Hz, 1H), 5.02 (d, 14Hz, 1H), 5.22 (m, 1H), 7.00-7.62 (m, 12H), 8.01 (m, 1H). FAB-MS: calculated for $C_{29}H_{32}N_6O_3$ 512; found 513 (M+1, 100%).

Step D: (R)-2-Amino-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]butanamide, hydrochloride

Prepared from the intermediate obtained in Step C by the method described in Example 1, Step I. ^{1}H NMR (200 MHz, CD_3OD): 0.83 (t, 7Hz, 3H), 1.68 (m, 2H), 3.80 (m, 1H), 4.81 (d, 14Hz, 1H), 5.01 (d, 14Hz, 1H), 7.00-7.70 (m, 13H). FAB-MS: calculated for $C_{24}H_{24}N_6O$ 412; found 413 (M+1, 100%).

Step E: 3-t-Butoxycarbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 3, Step F) and N-hydroxysuccinimde by the procedure describe in Example 1, Step M. ^{1}H NMR (200 MHz, $CDCl_3$): 1.41 (s, 9H), 1.43 (s, 6H), 2.82 (s, 4H), 3.07 (s, 2H), 4.72 (br s, 1H).

Step F: (R)-2-[(3-t-Butoxycarbonylamino-3-methyl-1-oxobutyl)-amino]-N-phenyl-N-[[2'-(1H-tetra-zol-5-yl)[1,1'-biphenyl]-4yl]methyl]-butanamide

Prepared as in Example 1, Step N from (R)-2-amino-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]butanamide, hydrochloride and 3-t-butoxycarbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester. ^{1}H NMR (200 MHz, CD_3OD): 0.74 (t, 7Hz, 3H), 1.32 (s, 6H), 1.40 (s, 9H), 1.58 (m, 2H), 2.45 (d, 13Hz, 1H), 2.58 (d, 13Hz, 1H), 4.29 (m, 1H), 4.78 (d, 14Hz, 1H), 4.95 (d, 14Hz, 1H), 6.97-7.79 (m, 13H). FAB-MS: calculated for $C_{34}H_{41}N_7O_4$ 611; found 612 (M+1, 100%).

Step G: (R)-2-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step F by the procedure described in Example 3, Step H. ^{1}H NMR (200 MHz, CD_3OD): 0.72 (t, 7Hz, 3H), 1.32 (s, 3H), 1.40 (s,

3H), 1.58 (m, 2H), 2.51 (m, 2H), 4.28 (m, 1H), 4.73 (d, 14Hz, 1H), 4.99 (d, 14Hz, 1H), 6.95-7.83 (m, 13H). FAB-MS: calculated for $C_{29}H_{33}N_7O_2$ 511; found 512 (M+1, 100%).

EXAMPLE 5

2-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]acetamide, trifluoroacetate

Step A: 2-t-Butoxycarbonylamino-N-[[2'-(N-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]acetamide

Prepared from N-triphenylmethyl-5-[2-(4'-aminomethyl-biphen-4-yl)]tetrazole (Example 1, Step F) and N-BOC-glycine by the procedure described in Example 1, Step G. ^1H NMR (200 MHz, $CDCl_3$): 1.43 (s, 9H), 3.72 (d, 5Hz, 2H), 4.32 (d, 6Hz, 2H), 5.06 (m, 1H), 6.30 (m, 1H), 6.82-7.68 (m, 22H), 7.95 (m, 1H).

Step B: 2-t-Butoxycarbonylamino-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]acetamide

Prepared from the intermediate obtained in Step A by the procedure described in Example 1, Step H. ^1H NMR (200 MHz, CD_3OD): 1.42 (s, 9H), 3.69 (s, 2H), 4.38 (d, 6Hz, 2H), 6.90-7.28 (m, 4H), 7.42-7.69 (m, 4H). FAB-MS: calculated for $C_{21}H_{24}N_6O_3$, 408; found 409 (M+1, 20%).

Step C: 2-Amino-N-[[2'-(1H-tetrazol-5-yl)[1,1'-bi-phenyl]-4-yl]methyl]acetamide, hydrochloride

Prepared from the intermediate obtained in Step B by the procedure described in Example 1, Step I. ^1H NMR (200 MHz, CD_3OD): 3.84 (s, 2H), 4.35 (s, 2H), 7.10-7.83 (m, 8H). FAB-MS: calculated for $C_{16}H_{16}N_6O$ 308; found 309 (M+1, 100%).

Step D: 2-[(3-Benzyloxycarbonylamino-3-methyl-1-oxo-butyl)-amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4yl]-methyl]acetamide

Prepared from the intermediate obtained in Step C and 3-benzyloxycarbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester by the procedure described in Example 1, Step N. ^{1}H NMR (200 MHz, CD_3OD): 1.37 (s, 6H), 2.60 (s, 2H), 3.79 (s, 2H), 4.33 (s, 2H), 5.00 (s, 2H), 6.95-7.65 (m, 13H). FAB-MS: calculated for $C_{26}H_{33}N_7O_4$ 507; found 508 (M+1, 20%).

Step E: 2-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]acetamide, trifluoroacetate

Prepared from the intermediate obtained in Step D by the procedure described in Example 1, Step O. ^{1}H NMR (200 MHz, CD_3OD): 1.38 (s, 6H), 2.52 (s, 2H), 3.89 (s, 2H), 4.38 (s, 2H), 7.00-7.70 (m, 8H). FAB-MS: calculated for $C_{21}H_{25}N_7O_2$ 407; found 408 (M+1,100%).

EXAMPLE 6

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methyl-amino)carbonyl]amino][1,1'-biphenyl]-4-yl]-methyl]-1H-indole-3-propanamide, trifluoroacetate

Step A: N-(t-Butoxycarbonyl)-D-tryptophan benzyl ester

Finely divided t-butoxycarbonyl-D-tryptophan (3 g, 10 mmol) was suspended in methylene chloride and benzyl alcohol (1.08 mL, 10 mmol) and 4-dimethylaminopyridine (0.12 g, 1 mmol) were added and stirred at room temperature. Solid 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (1.92 g, 10 mmol) was then added in three roughly equal portions over 5 minutes. The reaction mixture was stirred for 3 hours at room temperature during which time the reaction mixture became a homogeneous solution. The reaction

mixture was poured into water (100 mL) and extracted with methylene chloride (2 x 50 mL). The combined methylene chloride layers were washed with 5% aqueous citric acid solution (100 mL) and 5% aqueous sodium bicarbonate solution (100 mL). The resulting methylene chloride layer was dried over magnesium sulfate, filtered and evaporated under vaccum to give an off-white solid. This solid material was chromatographed on silica gel using ethyl acetate/hexanes (2:3 v/v) as eluant. This afforded 3.56 g (91%) of the desired benzyl ester as a white amorphous powder.
^{1}H NMR (400 MHz, $CDCl_3$): 1.42 (s, 9H), 3.27 (d, 2H), 4.69 (m, 1H), 5.17 (ABq, 2H), 6.78 (br s, 1H), 7.15-7.42 (m, 8H), 7.53 (d, 1H), 7.97 (br s, 1H).

Step B: D-Tryptophan benzyl ester

N-(t-Butoxycarbonyl)-D-tryptophan benzyl ester (3.5 g, 8.87 mmol) was dissolved in methylene chloride (10 mL) and stirred at room temperature and trifluoroacetic acid (20 mL) was added dropwise to the ester. The reaction mixture was stirred at room temperature for one hour during which time the reaction darkened. The reaction mixture was directly evaporated under vacuum to give a white solid. This solid was dissolved in chloroform (100 mL) and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with chloroform (2 x 25 mL) and the combined chloroform layers were dried over potassium carbonate. Filtration and concentration of the chloroform solution under vacuum gave a pale yellow oil (3.14 g, 82%) which was mainly the desired product.
^{1}H NMR (400 MHz, $CDCl_3$): 1.58 (s, 9H), 3.09 (dd, 1H), 3.27 (dd, 1H), 3.88 (m, 1H), 5.10 (s, 2H), 6.93 (br s, 1H), 7.15-7.39 (m, 8H), 7.59 (d, 1H), 8.03 (br s, 1H).

Step C: (R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-1H-indole-3-propanoic acid, benzyl ester

Crude D-tryptophan benzyl ester (1.0 g, 3.40 mmol), 1-hydroxybenztriazole hydrate (0.63 g, 4.1 mmol) and t-butoxycarbonyl-

α-methylalanine (0.84 g, 4.11 mmol) were stirred together at room temperature in chloroform (20 mL). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (980 mg, 5.11 mmol) was added to this mixture in a single portion. The reaction mixture was stirred at room temperature for 4 hours and worked up by pouring into water (50 mL). The chloroform layer was separated and washed with 5% aqueous citric acid solution (25 mL) and 5% aqueous sodium bicarbonate solution (25 mL). The chloroform layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a thick oily foam. Chromatography on silica gel using ethyl acetate/hexanes (2:3 v/v) afforded a yellow foam (0.822 g 50%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.30 (s, 9H), 1.39 (s, 6H), 3.29 (m, 2H), 4.88 (m, 1H), 5.03 (s, 2H), 6.88 (br s, 1H), 7.05-7.35 (m, 8H), 8.53 (d, 1H), 7.98 (br s, 1H).

<u>Step D</u>: <u>(R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-1H-indole-3-propanoic acid</u>

The benzyl ester (0.82 g, 1.71 mmol) obtained in Step C and 10% palladium on carbon (150 mg) were stirred together in ethyl acetate (5 mL). The solution was degassed and a hydrogen atmosphere introduced over the reactants using a balloon for 32 hours. The reaction products were isolated by filtering the reaction mixture through a Celite plug. The plug was washed with additional ethyl acetate (3 x 10 mL). The combined filtrates were evaporated under vacuum to afford the product (680 mg, 102%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.30 (s, 9H), 1.41 (s, 6H), 3.32 (dd, 1H), 3.42 (m, 1H), 4.87 (br s, 1H), 6.82 (d, 1H), 7.13-7.35 (m, 8H), 7.60 (d, 1H), 8.28 (br s, 1H).

<u>Step E</u>: <u>4-Methyl-2'-nitro-1,1'-biphenyl</u>

A vigorously stirred mixture of 34 g (0.25 mol) of 4-tolylboronic acid and 34 g (0.17 mol) of 2-bromo-1-nitrobenzene in a mixture of 170 mL of 5<u>N</u> sodium hydroxide, 57 mL of water, 215 mL of 2-propanol and 1080 mL of benzene was treated with 11.9 g of

(tetrakis)triphenylphosphine palladium(0). The two-phase mixture was heated at reflux for three hours. The cooled reaction mixture was filtered through Celite and the filter cake washed with fresh benzene. The organic layer was separated and washed with water (3x), dried over magnesium sulfate and filtered. The filtrate was evaporated under vacuum and the residue (46.1 g) purified by preparative high pressure liquid chromatography on silica gel, eluting with hexane/ethyl acetate (20:1), to give 28.05 g of the product. ^{1}H NMR (400 MHz, $CDCl_3$): 2.38 (s, 3H), 7.20 (m, 4H), 7.43 (m, 2H), 7.59 (t, 1H), 7.8 (d, 1H). EI-MS: calculated for $C_{13}H_{11}NO_2$ 213; found 213 (M^+).

<u>Step F</u>: <u>4-Bromomethyl-2'-nitro-1,1'-biphenyl</u>

Prepared from 4-methyl-2'-nitro-1,1'-biphenyl by the procedure described in Example 1, Step D. ^{1}H NMR (200 MHz, $CDCl_3$): 4.53 (s, 2H), 7.2-7.7 (m, 7H), 7.85 (m, 1H).

<u>Step G</u>: <u>4-Azidomethyl-2'-nitro-1,1'-biphenyl</u>

Prepared from 4-bromomethyl-2'-nitro-1,1'-biphenyl by the procedure described in Example 1, Step E. ^{1}H NMR (200 MHz, $CDCl_3$): 4.39 (s, 2H), 7.2-7.7 (m, 7H), 7.85 (d, 1H).

<u>Step H</u>: <u>4-Aminomethyl-2'-nitro-1,1'-biphenyl</u>

Prepared from 4-azidomethyl-2'-nitro-1,1'-biphenyl by the procedure described in Example 1, Step E. ^{1}H NMR (200 MHz, $CDCl_3$): 3.90 (s, 2H), 7.2-7.7 (m, 7H), 7.83 (d, 1H).

<u>Step I</u>: <u>(R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-N-[[(2'-nitro)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide</u>

The acid (338 mg, 0.87 mmol) from Step D and 4-aminomethyl-2'-nitro-1,1'-biphenyl (200 mg, 0.87 mmol) and triethylamine (0.245 mL, 1.76 mmol) were dissolved in methylene chloride (8 mL) and stirred at room temperature. Benzotriazolyl-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (388 mg,

0.87 mmol) was added in a single portion. The reaction mixture was stirred togerther for 3.5 hours then the reaction was quenched by adding saturated aqueous sodium chloride (10 mL) and extracted with methylene chloride (3 x 20 mL). The combined extracts were dried over magnesium sulfate, filtered and evaporated under vacuum. The resulting thick gum was chromatographed on silica gel using ethyl acetate/hexanes (1:2 v/v) to give 297 mg (50%) of an orange semi-solid. ^{1}H NMR (400 MHz, CD_3OD): 1.08 (s, 9H), 1.26 (s, 3H), 1.32 (s, 3H), 3.29 (dd, 1H), 3.43 (dd, 1H), 4.35 (m, 2H), 4.64 (m, 1H), 7.00-7.20 (m, 7H), 7.34 (d, 1H), 7.42 (m, 1H), 7.53 (t, 1H), 7.61 (d, 1H), 7.67 (t, 1H), 7.83 (d, 1H), 8.22 (s, 1H).

Step J: (R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-N-[[(2'-amino)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

The amide (142 mg, 0.24 mmol) from Step I was dissolved in ethanol (5 mL) and 10% palladium on carbon (15 mg) was added. The ethanolic mixture was degassed and a hydrogen atmosphere introduced and maintained above the reaction mixture for 2.5 hours using a balloon. The hydrogenation catalyst was removed by filtration through a Celite pad. The pad was washed carefully with methylene chloride (4 x 5 mL). The combined filtrates were evaporated under vacuum to give a powdery white foam (124 mg, 92%). ^{1}H NMR (400 MHz, CD_3OD): 1.09 (s, 9H), 1.26 (s, 3H), 1.31 (s, 3H), 3.29 (m, 1H), 3.43 (dd, 1H), 4.36 (m, 2H), 4.62 (m, 1H), 6.87 (m, 2H), 7.00-7.45 (m, 10H), 7.60 (d, 1H), 8.20 (s, 1H). FAB-MS: calculated for $C_{33}H_{39}N_5O_4$ 569; found 570 (M+1).

Step K: (R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-N-[[2'-[[(methylamino)-carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

The amine (25 mg, 0.04 mmol) from Step J was dissolved in methylene chloride and methyl isocyanate (0.009 mL, 0.15 mmol) was added to the amine. The reaction mixture was stirred together at

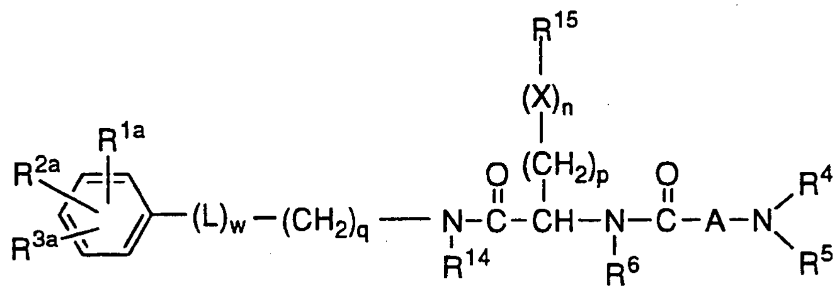
room temperature for 2.5 hours then the volatiles were removed directly under vacuum. The resultant residue was chromatographed on silica gel using ethyl acetate/hexanes (4:1 v/v) to afford the desired product (23 mg, 82%). ^{1}H NMR (200 MHz, CD_3OD): 1.10 (s, 9H), 1.24 (s, 3H), 1.30 (s, 3H), 2.64 (d, 3H), 3.33 (ABq, 2H), 4.33 (m, 2H), 4.60 (m, 1H), 6.23 (m, 1H), 6.96-7.45 (m, 11H), 7.58 (d, 1H), 7.68 (m, 1H), 8.20 (m, 1H). FAB-MS: calculated for $C_{35}H_{42}N_6O_5$ 626; found 627 (M+1).

Step L: (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[(methylaminocarbonyl)amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide, trifluoroacetate

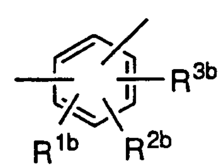
The intermediate obtained in Step K (15 mg, 0.023 mmol) and anisole (0.01 mL, 0.09 mmol) were dissolved in methanol (0.5 mL) and hexanes (0.5 mL). To this solution 0.5 mL of 9 N aqueous hydrochloric acid was added. The reactants were stirred at room temperature for 30 minutes then the hexane layer was removed using a pipette. The aqueous methanolic layer was evaporated at atmospheric pressure using a fast stream of nitrogen at room temperature. The solid material thus obtained was purified by reverse phase medium pressure liquid chromatography on C8, eluting with methanol/0.1% aqueous trifluoroacetic acid (85:15 v/v). This afforded 11.3 mg (0.018 mmol, 74%) of the title compound. ^{1}H NMR (400 MHz, CD_3OD): 1.38 (s, 3H), 1.56 (s, 3H), 2.66 (s, 3H), 3.18 (dd, 1H), 3.33 (dd, 1H), 4.35 (ABq, 2H), 4.78 (t, 1H), 6.98-7.47 (m, 10H), 7.62 (d, 1H), 7.64 (d, 1H). FAB-MS: calculated for $C_{30}H_{34}N_6O_3$ 526; found 527 (M+1).

WHAT IS CLAIMED IS:

1. A compound having the formula:



where L is



n is 0 or 1;
p is 0 to 6;
q is 0 to 4;
w is 0 or 1;

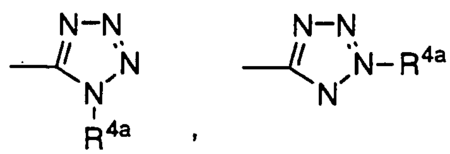
X is C=O, O, $S(O)_m$, $-\overset{\overset{\text{OH}}{|}}{\text{CH}}-$, $-\overset{\overset{\text{R10}}{|}}{\text{N}}-$, -CH=CH-;
m is 0 to 2;

R1, R2, R1a, R2a, R1b, and R2b are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_3 perfluoroalkoxy, $-S(O)_m$-R^{7a}, cyano, nitro, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, R^4R^5-$NCOO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy; R^{7a}

and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy and v is 0 to 3;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is



, ,

$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^{7b}O(CH_2)_vCO$-, $R^{4b}R^{12c}N(CH_2)_v$-, $R^{12a}R^{12b}NCO(CH_2)_v$-, $R^{12a}R^{12b}NCS(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CO(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CS(CH_2)_v$-, $R^{4b}R^{12a}NCON(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NCSN(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CON(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CSN(R^{12c})(CH_2)_v$-, $^{4b}R^{12a}NN(R^{12b})$-COO-$(CH_2)_v$-, $R^{4b}R^{12a}NCOO(CH_2)_v$-, or $R^{13}OCON(R^{12c})(CH_2)_v$-, where v is 0 to 3;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}, OR^{5a}, or COR^{5a}; R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{12a} and R^{12c}, or R^{4b} and R^{12a}, or R^{4b} and R^{12a}, or R^{4b} and R^{12c}, or R^{13} and R^{12c}, can be taken together to form $-(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 3 and R^1 and R^{10} are as defined;

R^{13} is C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are hydroxy, $-NR^{10}R^{11}$, carboxy, phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents

on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy where R^{10} and R^{11} are as defined;

R^{14} is hydrogen, R^1, R^2 independently disubstituted phenyl, C_1-C_{10} alkyl or substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5 alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl or $-NR^{10}R^{11}$ where R^1, R^2, R^{10} and R^{11} are as defined;

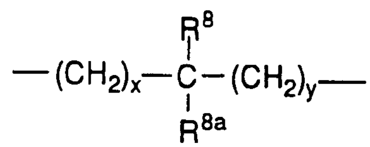
R^{15} is hydrogen, trifluoromethyl, R^1, R^2 independently disubstituted phenyl, R^1, R^2 independently disubstituted naphthyl, C_3-C_7 cycloalkyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted naphthyl, R^1, R^2 independently disubstituted naphthyl C_1-C_3 alkoxy, C_1-C_5 alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ or R^1, R^2 independently disubstituted heterocycle, where the heterocycle is imidazole, thiophene, furan, pyrrole, oxazole, thiazole, triazole, tetrazole, pyridine, benzofuran, benzothiophene, benzimidazole, indole, 7-azaindole, oxindole or indazole; where R^1, R^2, R^{10} and R^{11} are as defined above.

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_3-C_{10} alkenyl, substituted C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, or substituted C_3-C_{10} alkynyl where the substituents on the phenyl, alkyl, alkenyl or alkynyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, fluoro, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, phenyl C_1-C_6 alkyl, C_1-C_5-

alkoxycarbonyl or C_1-C_5-alkanoyl-C_1-C_6 alkyl; or R^4 and R^5 can be taken together to form -$(CH_2)_rB(CH_2)_s$- where B, r, s, R^1, R^{10} as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl, phenyl or phenyl C_1-C_{10} alkyl;

A is



where x and y are independently 0-3;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, trifluoromethyl, phenyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or -$NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above; or

R^8 and R^{8a} can be taken together to form -$(CH_2)_t$-where t is 2 to 6; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein:

n is 0 or 1;
p is 0 to 4;
q is 0 to 2;
w is 0 or 1;

X is O, $S(O)_m$, $-\overset{R^{10}}{\overset{|}{N}}-$, -CH=CH-;
m is 0 to 2;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl; phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is as defined in Claim 1.

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}, OR^{5a} or COR^{5a}; R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form $-(CH_2)_r-B-(CH_2)_s-$ where B is CHR', O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 3, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl, phenyl C_1-C_6 alkyl or C_1-C_5 alkanoyl -C_1-C_6 alkyl.

R^{13} is C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are hydroxy, $NR^{10}R^{11}$, carboxy, phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

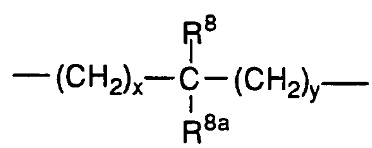
R^{14} and R^{15} are as defined in Claim 1;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl or phenyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy or formyl;

R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or N-R^{10}, r and s are independently 1 to 3 and R^1 and R^{10} are as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl or phenyl C_1-C_{10} alkyl;

A is



where x and y are independently 0-2;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, or C_1-C_5 alkanoyl-C_1-C_6 alkyl; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2 to 4; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms; and pharmaceutically acceptable salts thereof.

3. A compound of Claim 2 wherein:

n is 0 or 1;
p is 0 to 3;
q is 0 to 2;
w is 0 or 1;
X is O, $S(O)_m$, -CH=CH-;
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a} or OR^{5a}. R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form $-(CH_2)_r-B-(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 2, R^1 is as defined above, and R^{10} is hydrogen, C_1-C_6 alkyl or C_1-C_5 alkanoyl-C_1-C_6 alkyl;

R^{13} is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl or carboxy;

R^6 is hydrogen or C_1-C_{10} alkyl;

A is

$$-(CH_2)_x-\underset{R^{8a}}{\overset{R^8}{\underset{|}{\overset{|}{C}}}}-(CH_2)_y-$$

where x and y are independently 0-2;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2; or R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

4. A compound of Claim 3 wherein:

n is 0 or 1;
p is 0 to 2;
q is 1;
w is 1;
X is O, $S(O)_m$ or -CH=CH-;
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, -$S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 or 1;

R^{3a} and R^{3b} are independently hydrogen, R^9, or C_1-C_6 alkyl substituted with R^9;

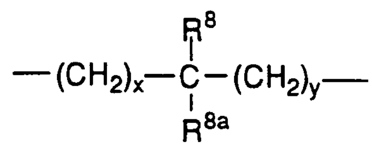
R^{12a}, R^{12b} and R^{12c} are independently R^{5a}. R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form -$(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 2, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl or C_1-C_5 alkanoyl-C_1-C_6 alkyl;

R^{13} is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^4, R^{4a}, R^{4b}, R^5, and R^{5a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 3 of hydroxy, C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20} alkanoyloxy, C_1-C_5 alkoxycarbonyl or carboxy;

R^6 is hydrogen;

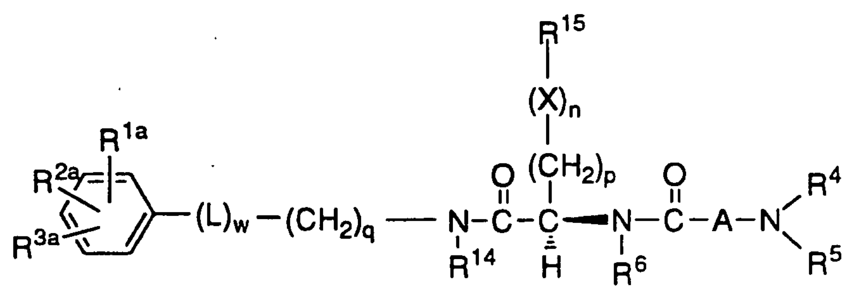
A is



where x and y are independently 0-1;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

5. A stereospecific compound of Claim 1 having the following structural formula:



Ia

where X, n, p, q, L, w, R^{1a}, R^{2a}, R^{3a}, R^4, R^5, R^6, R^{14}, R^{15}, and A are as defined in Claim 1

6. A compound of Claim 1 which is:

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]benzenebutanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzenebutanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]benzenepentanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzenepentanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-indole-3-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[(phenylmethyl)-oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[(phenylmethyl)-oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-4-phenylbutyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-4-phenylbutyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-5-phenylpentyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-5-phenylpentyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-5-phenylpentyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-5-phenylpentyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-[(phenylmethyl)oxy]propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-[(phenylmethyl)oxy]propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-1-oxo-3-[(phenylmethyl)-oxy]propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[(phenylmethyl)-oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-[[(2,6-difluorophenyl)methyl]oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-[[(2,6-difluorophenyl)methyl]oxy]-propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-1-oxo-3-[[(2,6-difluoro-phenyl)methyl]oxy]-propyl]amino]methyl]-N-ethyl-[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[[(2,6-difluoro-phenyl)methyl]oxy]-propyl]amino]methyl]-N-ethyl-[1,1'-biphenyl]-2-carboxamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methyl-amino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzene-butanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-a-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzenebutanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzenebutanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzenepentanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzenepentanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxy-methyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxy-methyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxy-methyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxy-methyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methyl-amino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-benzenepentanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methyl-amino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methyl-amino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

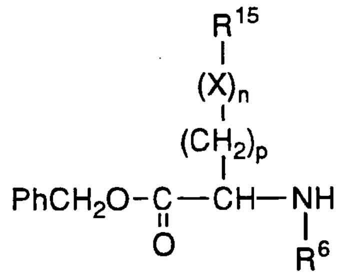
(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methyl-amino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluoro-phenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]-propanamide; or

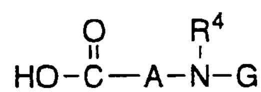
(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]-propanamide.

7. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:



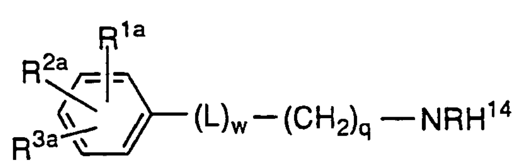
II

where R^6, R^{15}, X, n and p are as defined in Claim 1 with a compound having the formula:



III

where R^4 and A are defined in Claim 1 and G is a protecting group; which step is either followed by or preceded by the treatment of the compound with



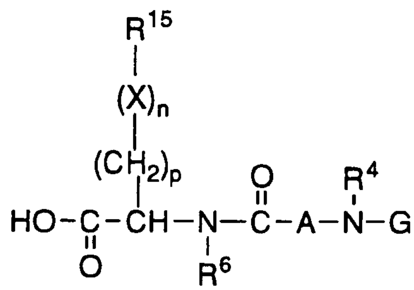
V

where R^{1a}, R^{2a}, R^{3a}, R^{14}, L, q and w are as defined in

Claim 1, followed by replacement of the protecting group G with R^5.

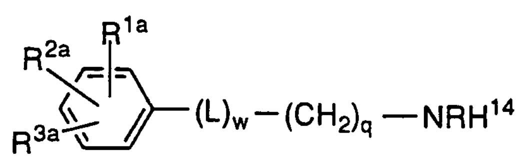
8. The process of Claim 7 where compound II is first reacted with compound III followed by reaction with compound V.

9. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:



IV

where R^4, R^6, R^{15}, A, X, n and p are as defined in Claim 1 and G is a protecting group, with a compound having the formula:



V

where R^{1a}, R^{2a}, R^{3a}, R^{14}, L, q and w are as defined in Claim 1, followed by replacement of the protecting group G with R^5.

10. The process of Claim 9 where the protecting group G is t-butoxycarbonyl or benzyloxycarbonyl.

11. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of a compound of Claim 1.

12. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1.

13. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim I used in combination with other growth hormone secretagogues such as, GHRP-6 or GHRP-1, growth hormone releasing factor (GRF) or one of its analogs, IGF-1 or IGF-2, or B-HT920.

14. A method for the treatment of obesity which comprises administering to an obese patient an effective amount of a compound of Claim 1 in combination with an α_2-adrenergic agonist or β_3-adrenergic agonist.

15. A composition for the treatment of obesity which comprises an inert carrier and an effective amount of a compound of Claim 1 in combination with an α_2-adrenergic agonist or β_3-adrenergic agonist.

16. A method for the treatment of osteoporosis which comprises administering to a patient with osteoporosis an effective amount of a compound of Claim 1 in combination with parathyroid hormone or a bisphosphonate.

17. A composition for the treatment of osteoporosis which comprises an inert carrier and an effective amount of a compound of Claim 1 in combination with parathyroid hormone or a bisphosphonate.

INTERNATIONAL SEARCH REPORT

International application No. PCT/US93/10551

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 37/00, 37/02, 37/36
US CL :514/002, 012, 021
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/002, 012, 021

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Int. J. Peptide Protein Res., Volume 38, issued 1991, K. Sato et al., "Solid Phase Synthesis of Human Growth Hormone-Releasing Factor Analogs Contianing a Bicyclic Beta-Turn Dipeptide", pages 340-345, see entire document.	1-17
A	Chem. Pharm. Bull., Volume 32, No. 3, issued 1984, N. Fujii et al., "Studies on Peptides. CXX. Synthesis of Growth Hormone Releasing Factor (GRF-37-NH2) and N-Biotinyl-GRF-44 NH2", pages 1200-1208, see entire document.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search	Date of mailing of the international search report
26 JANUARY 1994	04 FEB 1994

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	CAROL A. SALATA
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(54) Title: SPIRO PIPERIDINES AND HOMOLOGS WHICH PROMOTE RELEASE OF GROWTH HORMONE

(57) Abstract

There are disclosed certain novel compounds identified as spiro piperidines and homologs which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing such spiro compounds as the active ingredient thereof are also disclosed.

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TITLE OF THE INVENTION

SPIRO PIPERIDINES AND HOMOLOGS WHICH PROMOTE RELEASE OF GROWTH HORMONE

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body:

1. Increased rate of protein synthesis in all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be

administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recently, recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. The instant compounds are non-peptide analogs for promoting the release of growth hormone which are stable in a variety of physiological environments and which may be administered parenterally, nasally or by the oral route.

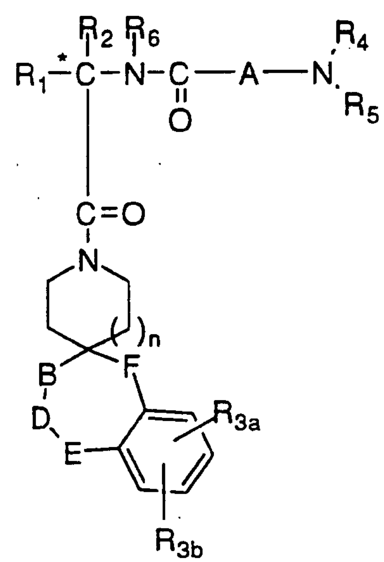
SUMMARY OF THE INVENTION

The instant invention covers certain spiro compounds which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the spiro compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the spiro compounds for the use of treating humans and animals so as to increase

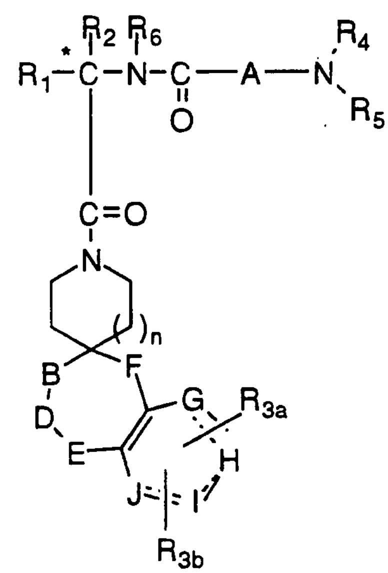
the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

The novel spiro compounds of the instant invention are best described in the following structural formulas I and II:



Formula I



Formula II

R_1 is C_1-C_{10} alkyl, aryl, aryl (C_1-C_6 alkyl) and C_3-C_7 cycloalkyl (C_1-C_6alkyl) or C_1-C_5alkyl-K-C_1-C_5 alkyl, aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl), C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl) where K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, OC(O), C(O)O, or $-CR_2=CR_2-$ or $-C\equiv C-$ where the aryl groups are defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a} or $C(O)OR_{2a}$ and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 OR_2, methylenedioxy, $S(O)_mR_2$, 1 to 2 CF_3, OCF_3, nitro, $N(R_2)(R_2)$, $N(R_2)C(O)R_2$, $C(O)OR_2$, $C(O)N(R_2)(R_2)$, $SO_2N(R_2)(R_2)$, $N(R_2)S(O)_2$ aryl or $N(R_2)SO_2R_2$;

R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

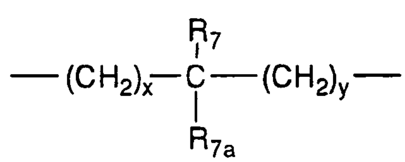
R_{2a} is hydrogen or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently hydrogen, halogen, C_1-C_6 alkyl, OR_2, cyano, OCF_3, methylenedioxy, nitro, $S(O)_mR$, CF_3 or $C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

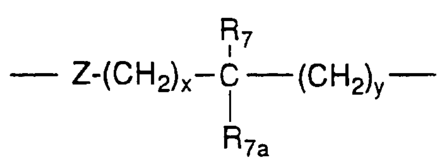
R_4 and R_5 are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form $-(CH_2)_rL_a(CH_2)_s-$ where L_a is $C(R_2)_2$, O, $S(O)_m$ or $N(R_2)$, r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



where x and y are independently 0-3;
Z is N-R_2 or O;
R_7 and R_{7a} are independently hydrogen, C_1-C_6 alkyl, OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR_2, 1 to 3 fluoro, $S(O)_mR_2$, $C(O)OR_2$, C_3-C_7 cycloalkyl, $N(R_2)(R_2)$, $C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently $C(R_8)(R_{10})$, O, C=0, $S(O)_m$, or NR_9, such that one or two of B,D,E, or F may be optionally missing to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be $C(R_8)(R_{10})$ or C=O only when one of the remaining B, D, E and F groups is simultaneously O, S(O)m or NR_9; B and D or D and E taken together may be $N{=}CR_{10}$- or $CR_{10}{=}N$ or B and D or D and E taken together may be $CR_8{=}CR_{10}$ provided one of the other of B and E or F is simultaneously O, $S(O)_m$ or NR_9;

R_8 and R_{10} are independently hydrogen, R_2, OR_2, $(CH_2)_q$ aryl, $(CH_2)_q$ $C(O)OR_2$, $(CH_2)_q$ $C(O)O(CH_2)_q$ aryl or $(CH_2)_q$ (1H-tetrazol-5-yl) and the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 OR_2 or 1 to 2 $C(O)OR_2$;

R_9 is R_2, $(CH_2)_q$ aryl, $C(O)R_2$, $C(O)(CH_2)_q$ aryl, SO_2R_2, $SO_2(CH_2)_q$ aryl, $C(O)N(R_2)(R_2)$, $C(O)N(R_2)(CH_2)_q$ aryl, $C(O)OR_2$, 1-H-tetrazol-5-yl, SO_3H, $SO_2NHC{\equiv}N$, $SO_2N(R_2)$aryl, $SO_2N(R_2)(R_2)$ and the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 OR_{2a}, $O(CH_2)_q$ aryl, 1 to 2 $C(O)OR_{2a}$, 1 to 2 $C(O)O(CH_2)_q$ aryl, 1 to 2 $C(O)N(R_{2a})(R_{2a})$, 1 to 2 $C(O)N(R_{2a})(CH_2)_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $C(O)NHSO_2R_{2a}$, $S(O)_mR_{2a}$, $C(O)NHSO_2(CH_2)_q$ aryl, $SO_2NHC{\equiv}N$, $SO_2NHC(O)R_{2a}$.

$SO_2NHC(O)(CH_2)_q$aryl, $N(R_2)C(O)N(R_{2a})(R_{2a})$, $N(R_{2a})C(O)N(R_{2a})(CH_2)_q$ aryl, $N(R_{2a})(R_{2a})$, $N(R_{2a})C(O)R_{2a}$, $N(R_{2a})C(O)(CH_2)_q$ aryl, $OC(O)N(R_{2a})(R_{2a})$, $OC(O)N(R_{2a})(CH_2)_q$ aryl; $SO_2(CH_2)_qCONH$-$(CH_2)_wNHC(O)R_{11}$, where w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;

n is 1 or 2;

q can optionally be 0, 1, 2, 3, or 4; and

G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that atleast one is a heteroatom and one of G, H, I or J may be optionally missing to afford 5 or 6 membered heterocyclic aromatic rings; and pharmaceutically acceptable salts and individual diastereomers thereof.

In the above structural formulas and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, ethinyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propenyl, butenyl, butadienyl and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propinyloxy, isobutenyloxy, 2-hexenyloxy, and the like.

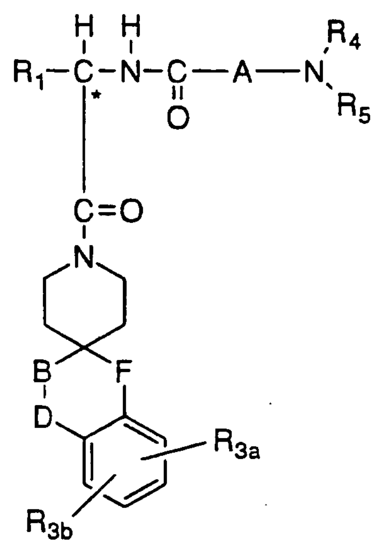
The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" is intended to include phenyl and naphthyl and aromatic residues of 5- and 6- membered rings with 1 to 3

heteroatoms or fused 5 or 6 membered bicyclic rings with 1 to 3 heteroatoms of nitrogen, sulfur or oxygen. Examples of such heterocyclic aromatic rings are pyridine, thiophene, benzothiophene, tetrazole, indole, N-methylindole, dihydroindole, indazole, N-formylindole, benzimidazole, thiazole, furan, pyrimidine, and thiadiazole.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Preferred compounds of the instant invention are:



Formula III

where R_1 is C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl), C_3-C_6 cycloalkyl (C_1-C_4 alkyl), (C_1-C_4 alkyl)-K-(C_1-C_4 alkyl), aryl(C_0-C_5alkyl)-K-(C_1-C_4 alkyl), (C_3-C_7cycloalkyl)(C_0-C_5 alkyl)-K-(C_1-C_4alkyl) where K is O, $S(O)_m$, $-CR_2{=}CR_2$-, -C≡C-, or $N(R_2)C(O)$ where R_2 and the alkyl groups may be further substituted by 1 to 7 halogen, $S(O)_mC_1$-C_4 alkyl, OR_{2a} or $C(O)OR_{2a}$ and the aryl groups may be further substituted by 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 OR_2,

CF_3, OCF_3, methylenedioxy, $S(O)_mR_2$, $SO_2N(R_2)(R_2)$, $N(R_2)SO_2R_2$ or $C(O)OR_2$;

R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_7cycloalkyl, and, if two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_4-C_6 cyclic ring optionally including 1 to 2 heteroatoms selected from oxygen, sulfur or NR_{2a};

R_{2a} is hydrogen or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently hydrogen, halogen, C_1-C_4 alkyl, OR_2, methylenedioxy, nitro, $S(O)_mC_1$-C_4alkyl, CF_3 or $C(O)OR_2$;

R_4 and R_5 are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 2 hydroxy, 1 to 2 C_1-C_6 alkanoyloxy, 1 to 2 C_1-C_6 alkyloxy or $S(O)_m(C_1$-C_4 alkyl);

A is :

$$-(CH_2)_x-\overset{\displaystyle R_7}{\underset{\displaystyle R_{7a}}{\overset{|}{\underset{|}{C}}}}-(CH_2)_y-$$

or

$$-N(R_2)\text{-}(CH_2)_x-\overset{\displaystyle R_7}{\underset{\displaystyle R_{7a}}{\overset{|}{\underset{|}{C}}}}-(CH_2)_y-$$

where x and y, are independently 0, 1, or 2;

R_7 and R_{7a} are independently hydrogen, C_1-C_4 alkyl, substituted

C_1-C_4 alkyl where the substituents are from 1 to 3 fluoro or imidazolyl, phenyl, indolyl, $S(O)_mC_1$-C_4alkyl, $C(O)OR_2$ or R_7 and R_{7a} can independently be joined to one or both of the R_4 and R_5 groups to form alkylene bridges between the teminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 3 carbon atoms;

B, D and F are independently $C(R_8)(R_{10})$, O, C=O, $S(O)_m$ or NR_9 such that one of B, D or F may be optionally missing to provide a 5 or 6 membered ring and provided that one of B, D and F is $C(R_8)(R_{10})$ or C=O only when one of the remaining B, D and F groups is simultaneously O, $S(O)_m$ or NR_9;

R_8 and R_{10} are independently hydrogen, R_2, OR_2, $(CH_2)_q$ aryl, $(CH_2)_qC(O)OR_2$, $(CH_2)_qC(O)O(CH_2)_q$ aryl, $(CH_2)_q$(1H-tetrazol-5-yl) and the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_4 alkyl, 1 to 3 OR_2 or 1 to 2 $C(O)OR_2$;

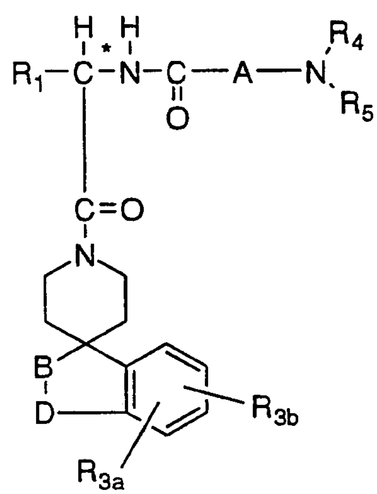
R_9 is R_2, $(CH_2)_q$ aryl, $C(O)R_2$, $C(O)(CH_2)_q$ aryl, SO_2R_2, $SO_2(CH_2)_q$ aryl, $C(O)N(R_2)(R_2)$, $C(O)N(R_2)(CH_2)_q$ aryl, 1-H-tetrazolyl-5-yl, $SO_2NHC{\equiv}N$, SO_2NR_2 aryl, $SO_2N(R_2)(R_2)$ and the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_2 alkyl and the R_2 may be optionally substituted by 1 to 2 OR_{2a}, $O(CH_2)_q$ aryl, 1 to 2 $C(O)OR_{2a}$, $C(O)N(R_{2a})(R_{2a})$, $S(O)_mR_{2a}$, 1-H-tetrazol-5-yl, $C(O)NHSO_2R_{2a}$, $C(O)NHSO_2(CH_2)_q$ aryl, $N(R_{2a})C(O)N(R_{2a})(R_{2a})$ or $N(R_{2a})C(O)N(R_{2a})(CH_2)_q$ aryl and the aryl may be optionally substituted by 1 to 2 OR_{2a}, 1 to 2 halogen, 1 to 2 C_1-C_4 alkyl, $C(O)OR_{2a}$ or 1-H-tetrazol-5-yl; $SO_2(CH_2)_w$ $CONH(CH_2)_w$ $NHC(O)R_{11}$, where w = 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0,1, or 2;
q can optionally be 0, 1, 2 or 3; and

the aryl group is phenyl, napthyl, pyridyl, thienyl, indolyl, thiazolyl or pyrimidinyl,
and the pharmaceutically acceptable salts and individual diastereomers thereof.

Still further preferred compounds are realized when F is not present in Compound III.

Thus, further preferred compounds of the instant invention are realized in structural formula IV.



IV

R_1 is C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl), C_5-C_6cycloalkyl (C_1-C_4 alkyl) or (C_1-C_4 alkyl)-K-C_1-C_2alkyl-, aryl(C_0-C_2alkyl)-K-(C_1-C_2 alkyl), C_3-C_6cycloalkyl (C_0-C_2alkyl)-K-(C_1-C_2alkyl), where K is O or $S(O)_m$, and the aryl groups may be further substituted by 1 to 2 C_1-C_4 alkyl, 1 to 2 halogen, OR_2, $C(O)OR_2$, CF_3 or $S(O)_mR_2$;

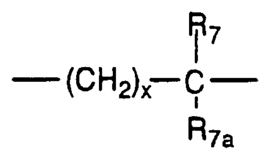
R_2 is hydrogen, C_1-C_4 alkyl, cyclo C_3-C_6alkyl, and, if two C_1-C_4 alkyls are present on one atom, they may be optionally joined to form a C_5-C_6 cyclic ring optionally including the heteroatoms oxygen or NR_{2a};

R_{2a} is hydrogen or C_1-C_4 alkyl;

R_{3a} and R_{3b} are independently hydrogen, halogen, C_1-C_4 alkyl, $C(O)OR_2$, hydroxy, C_1-C_4 alkoxy, $S(O)_mC_1$-C_4 alkyl or CF_3;

R_4 and R_5 are independently hydrogen, C_1-C_4 alkyl, substituted C_1-C_4 alkyl where the substituents may be 1 to 2 hydroxy or $S(O)_m$ (C_1-C_3alkyl);

A is:



where x is 0 or 1;

R_7 and R_{7a} are independently hydrogen, C_1-C_3 alkyl; or R_7 and R_{7a} can independently be joined to one or both of the R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups to form 5 or 6 membered rings containing the terminal nitrogen;

B and D are independently $C(R_8)(R_{10})$, C=O, O, $S(O)_m$, NR_9 provided that one of B and D can be $C(R_8)(R_{10})$ or C=O only when the other of B and D is O, $S(O)_m$ or NR_9;

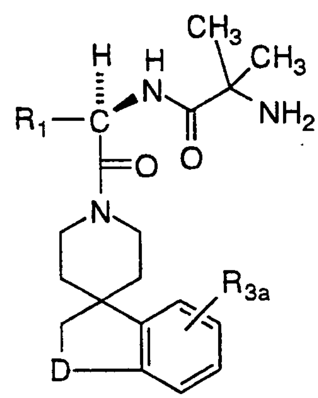
R_8 and R_{10} are independently hydrogen, R_2 or $(CH_2)_q$ aryl, and the aryl may be optionally substituted by 1 to 2 of halo, 1 to 2 C_1-C_4 alkyl, OR_2 or 1 to 2 $C(O)OR_2$;

R_9 is $C(O)R_2$, $C(O)(CH_2)_q$ aryl, SO_2R_2, $SO(CH_2)_q$ aryl, $C(O)N(R_2)(R_2)$, $C(O)N(R_2)(CH_2)_q$ aryl and the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_2 alkyl and the R_2 may be optionally substituted by 1 to 2 of OR_{2a}, $O(CH_2)_q$ aryl, $C(O)OR_{2a}$,

$C(O)N(R_{2a}(R_{2a})$, $S(O)_mR_{2a}$, 1-H-tetrazol-5-yl, $C(O)NHSO_2R_{2a}$, or $N(R_{2a})C(O)N(R_{2a})(R_{2a})$ and the aryl may optionally be substituted by 1 to 2 OR_{2a}, 1 to 2 halogen, 1 to 2 C_1-C_2 alkyl, $C(O)OR_{2a}$, 1-H-tetrazol-5-yl or $S(O)_mR_{2a}$;
$SO_2(CH_2)_qCONH(CH_2)_wNHC(O)R_{11}$ where w = 2-6 and R_{11} may optionally be biotin, aryl, and an aryl be optionally substituted by 1 to 2 OR_2, 1-2 halogen, azido, nitro;

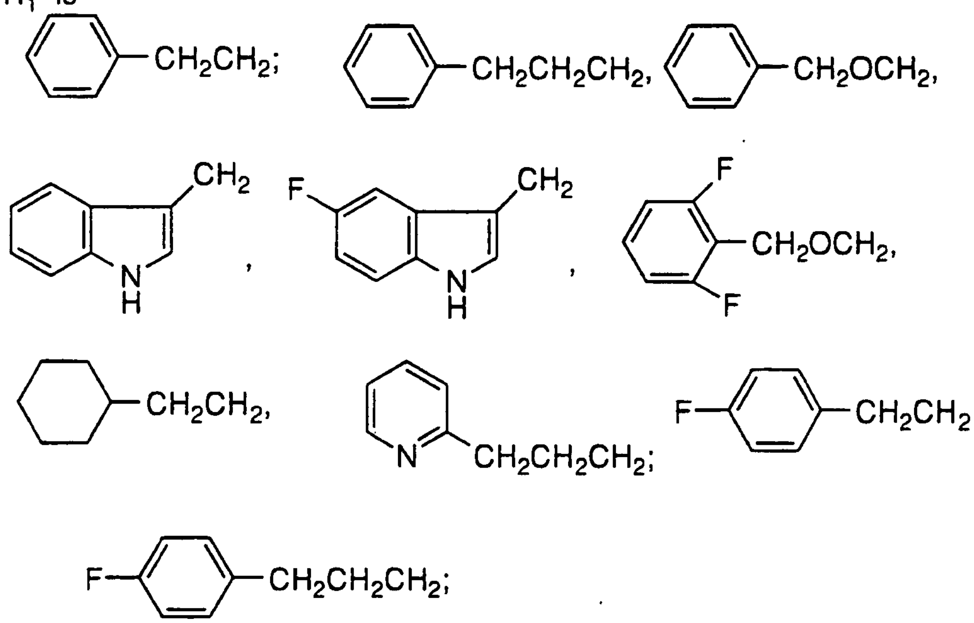
m is 0, 1 or 2;
q can optionally be 0, 1, 2 or 3;
aryl is phenyl, napthyl, pyridyl, indolyl, thienyl or tetrazolyl and the pharmaceutically acceptable salts and individual diastereomers thereof.

Most preferred compounds of the instant invention are realized in structural formula V:

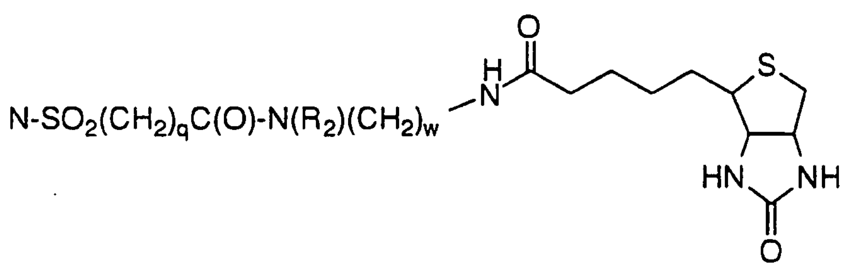


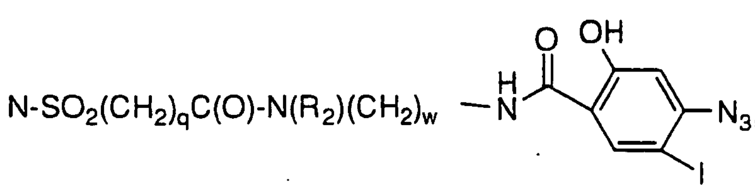
V

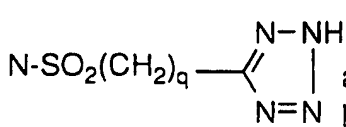
R_1 is



R3a is H, fluoro;
D is O, S, $S(O)_m$, $N(R_2)$, $NSO_2(R_2)$, $NSO_2(CH_2)_t$aryl, $NC(O)(R_2)$, $NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(R_2)$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(CH_2)_wOH$,

,



 and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;

R_2 is H, C_1-C_4 alkyl;
m = 1, 2;
t is 0, 1, 2;
q is 1, 2, 3;
w is 2-6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

Representative most preferred growth hormone releasing compounds of the present invention include the following:

1. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide

2. N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide

3. N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide

4. N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

5. N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide

6. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

7. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt

8. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

9. N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

10. N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide

11. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide

12. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide

13. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide

14. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

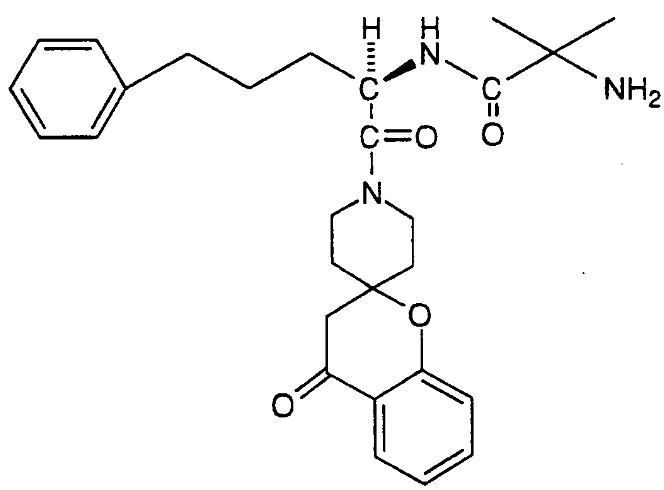
15. N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

16. N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

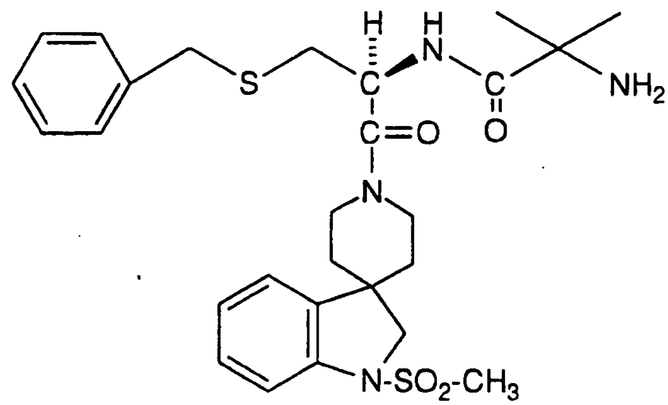
17. N-[1(R)-[(1,2-Dihydro-1,1dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

and pharmaceutically acceptable salts thereof.

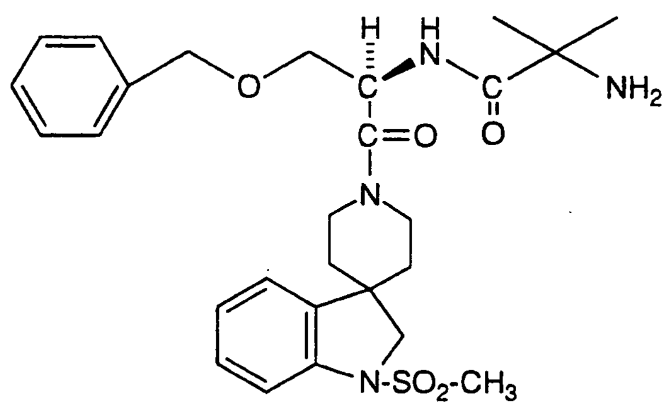
Representative examples of the nomenclature employed are given below:



N-[1(R)-[(3,4-Dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamide



\N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide



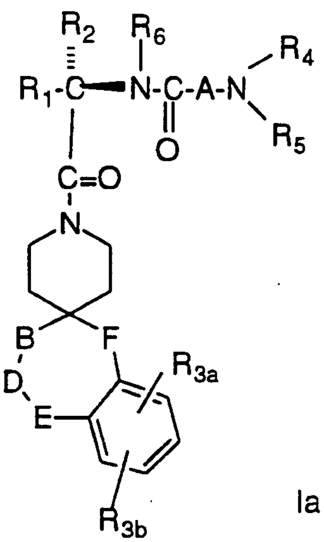
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

Throughout the instant application, the following abbreviations are used with the following meanings:

BOC	t-butyloxycarbonyl
BOP	Benzotriazol-1-yloxy tris/dimethylamino)-phosphonium hexafluorophosphate
CBZ	Benzyloxycarbonyl
DCC	Dicyclohexylcarbodiimide
DMF	N,N-dimethylformamide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride
FAB-MS	Fast atom bombardment-mass spectroscopy
GHRP	Growth hormone releasing peptide
HOBT	Hydroxybenztriazole
LAH	Lithium aluminum hydride
HPLC	High pressure liquid chromatography
MHz	Megahertz
MPLC	Medium pressure liquid chromatography
NMM	N-Methylmorpholine
NMR	Nuclear Magnetic Resonance
OXONE	Potassium peroxy monosulfate
PLC	Preparative layer chromatography
PCC	Pyridinium chlorochromate
Ser	Serine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formulas I and II above. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or diastereomeric mixtures thereof, be included within the ambit of the

instant invention. In the case of the asymmetric center represented by the asterisk in Formula I and II, it has been found that the absolute stereochemistry of the more active and thus more preferred isomers are as shown in Formula Ia. With the R2 substituent as hydrogen, the special configuration of the asymmetric center corresponds to that in a D-amino acid. In most cases this is also designated an R-configuration although this will vary according to the values of R1 and R2 used in making R- or S stereochemical assignments.



Ia

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

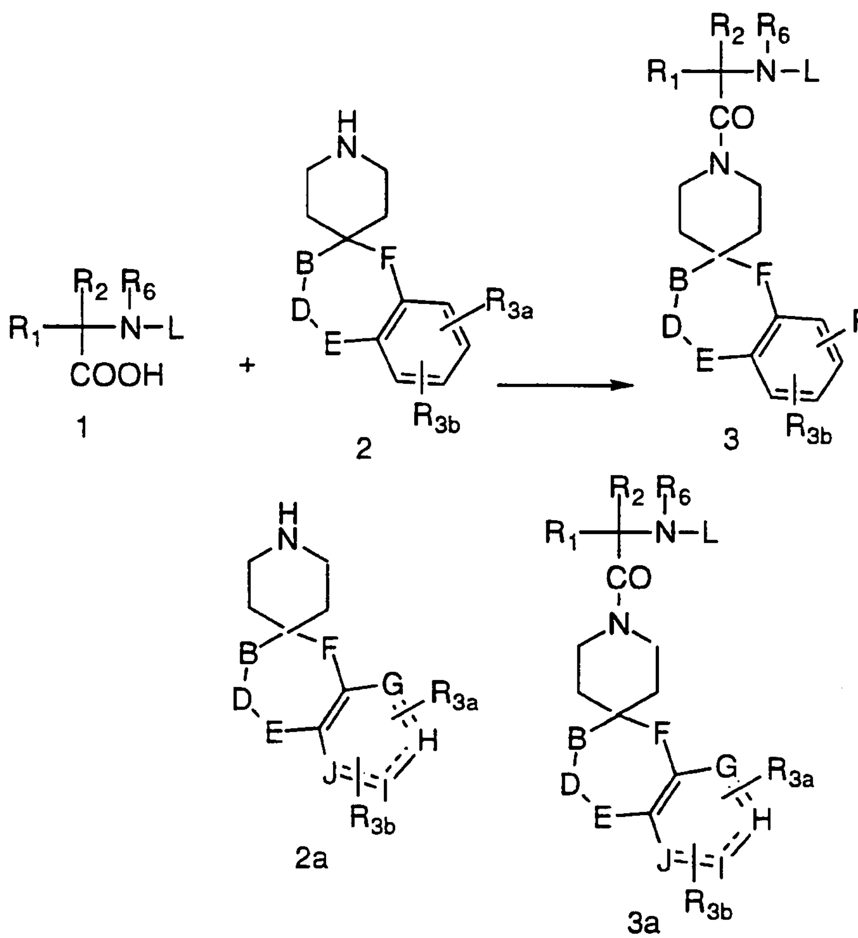
The preparation of compounds **I** and **II** of the present invention can be carried out in sequential or convergent synthetic

routes. Syntheses detailing the preparation of the compounds of Formula **I** and **II** in a sequential manner are presented in the following reaction schemes.

The protected amino acid derivatives **1** are, in many cases, commercially available where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives **1** can be prepared by literature methods. Many of the spiro piperidines and spiroazepines (n=2) of formula **2** and **2a** are known in the literature and can be derivatized on the phenyl or heteroaryl by standard means, such as halogenation, nitration, sulfonylation, etc. Alternatively, various phenyl or heteroaryl substituted spiro piperidines and spiroazepines (n=2) can be prepared following literature methods using derivatized phenyl and heterаryl intermediates. In Schemes subsequent to Scheme I, the synthetic methods are illustrated only with spiropiperidines although it will be appreciated by those skilled in the art that the illustrated transformations can also be carried out in the higher homolog series to afford compounds of Formulas I and II with n=2.

Intermediates of formulas **3** and **3a** can be synthesized as described in Scheme 1. Coupling of spiro piperidines of formula **2** and **2a** to protected amino acids of formula **1**, wherein L is a suitable protecting group, is conveniently carried out in an inert solvent such as dichloromethane by a coupling reagent such as DCC or EDC in the presence of HOBT. Alternatively, the coupling can also be effected with a coupling reagent such as BOP in an inert solvent such as dichloromethane. Separation of unwanted side products, and purification of intermediates is achieved by chromatography on silica gel, employing flash chromatography (W. C. Still, M. Kahn, and A. Mitra *J. Org. Chem.* **1978**, *43*, 2923), MPLC or preparative TLC.

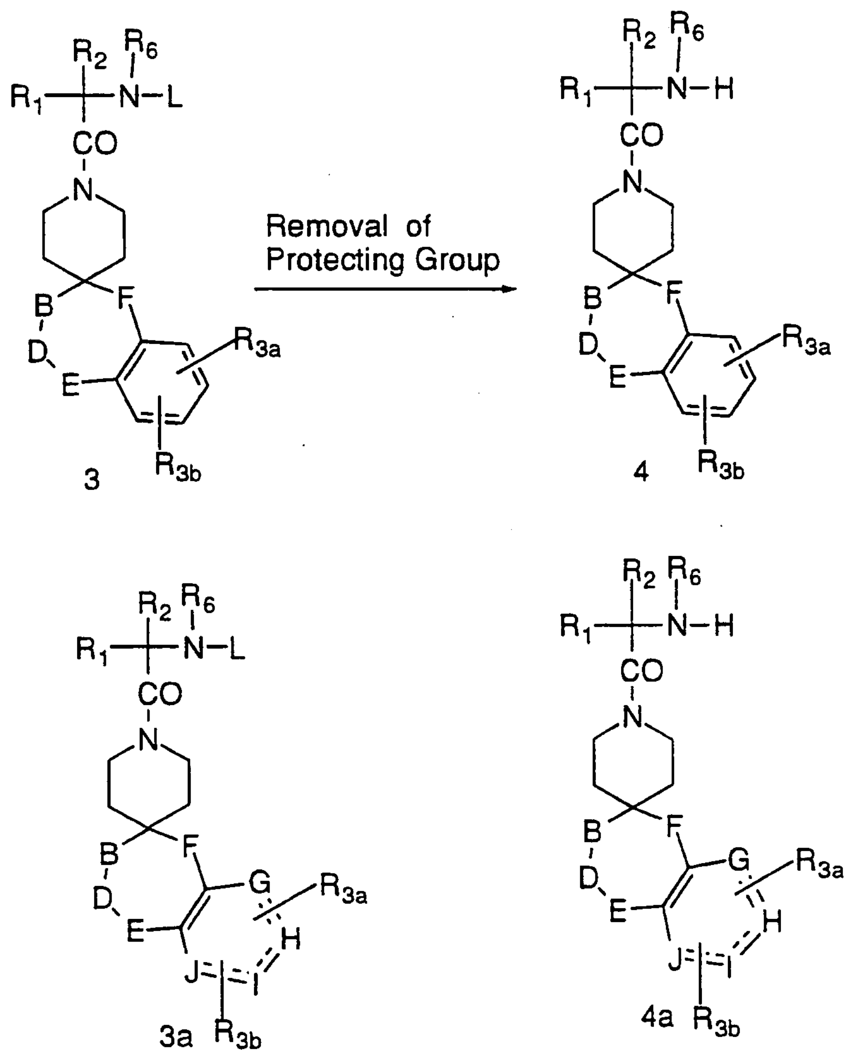
SCHEME 1



Conversion of **3** and **3a** to intermediates **4** and **4a** can be carried out as illustrated in Scheme 2. Removal of benzyloxycarbonyl groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of palladium or platinum catalyst in a protic solvent such as methanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of benzyloxy carbonyl groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or methanol, with a strong acid, such as hydrochloric acid or trifluoroacetic acid. Conditions required to remove other protecting groups which may be

present can be found in Greene, T; Wuts, P.G.M. *Protective Groups in Organic Synthesis* , John Wiley & Sons, Inc., New York, NY 1991.

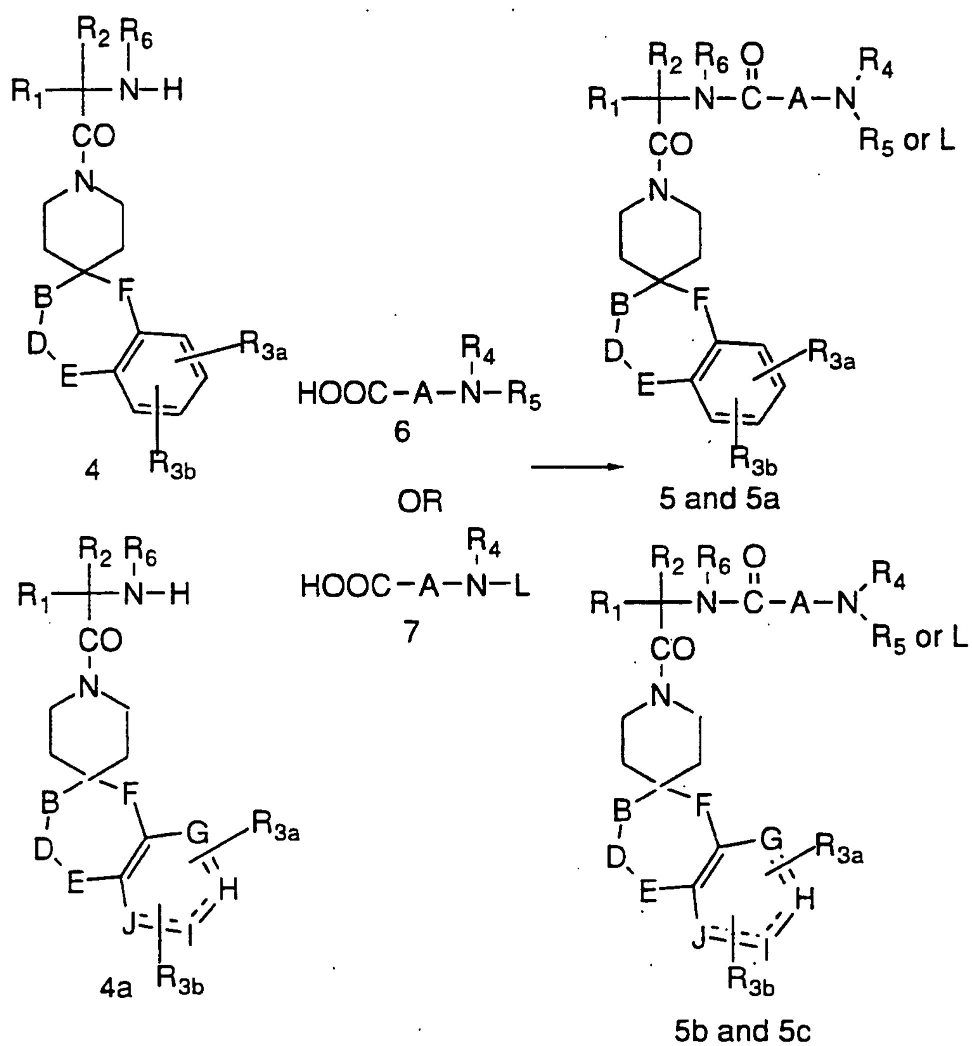
SCHEME 2



Intermediates of formula **5** and **5b**, wherein A is a methylene or a substituted methylene group, can be prepared as shown in Scheme 3 by coupling of intermediates of formula **4** and **4a** to amino acids of formula **6**, once again, in an inert solvent such as dichloromethane by a coupling reagent such as EDC or DCC in the presence of HOBT. These amino acids 6 are known amino acids or

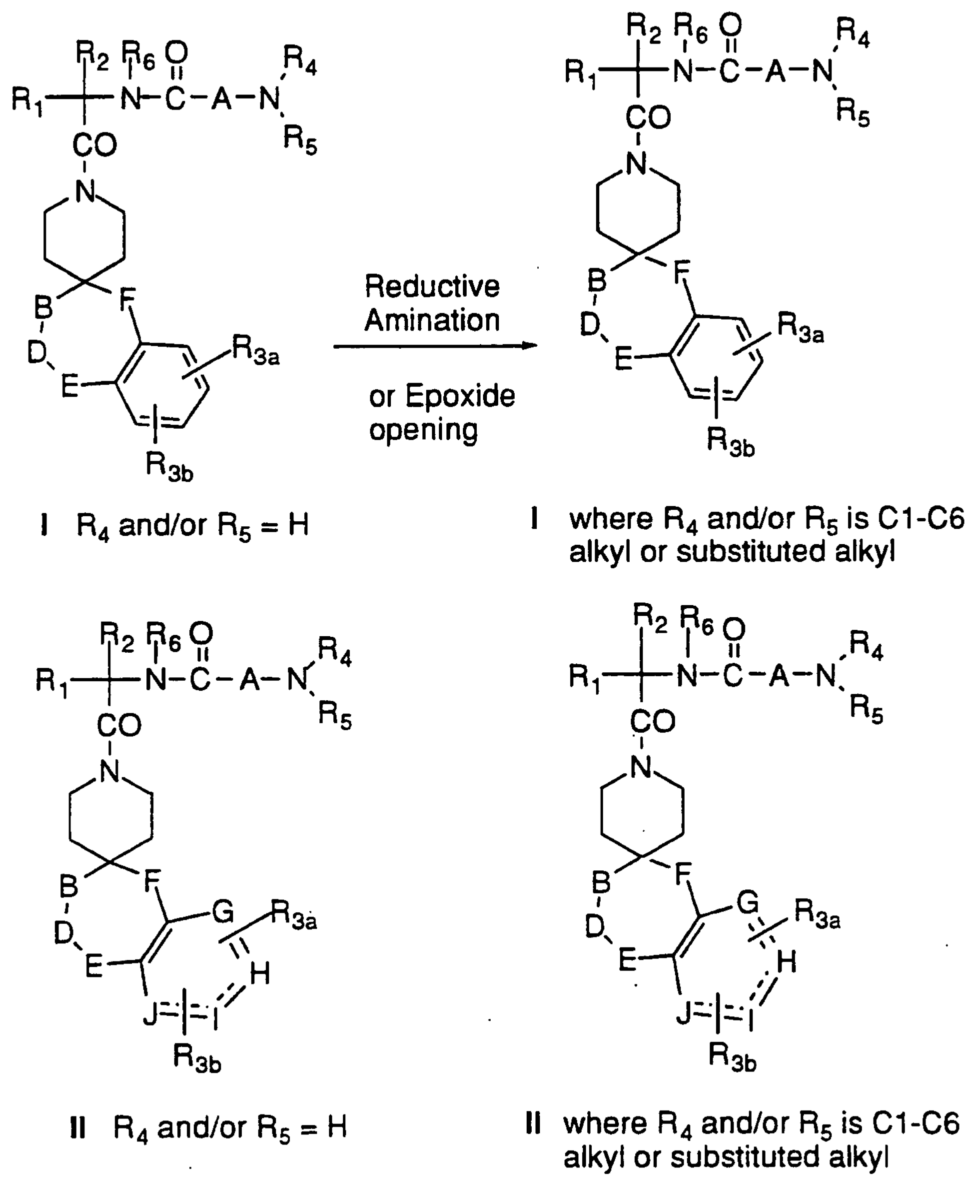
amino acids readily synthesized by methods known to those skilled in the art. Alternatively, the coupling can also be effected with a coupling reagent such as BOP in an inert solvent such as dichloromethane. Also if R4 or R5 is a hydrogen then amino acids of formula **7** are employed in the coupling reaction, wherein L is a protecting group as defined above, to give **5a** and **5c**. Deprotection of **5a** and **5c** (L = protecting group) can be carried out under conditions known in the art.

SCHEME 3



Compounds of formula **I** and **II** wherein R_4 and/or R_5 is a hydrogen can be further elaborated to new compounds **I** and **II** (preferred side chain $R_7 = CH_2\text{-}CH(OH)\text{-}CH_2X$, wherein X = H or OH) which are substituted on the amino group as depicted in Scheme 4. Reductive amination of **I** and **II** with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in an inert solvent such as methanol or ethanol. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.

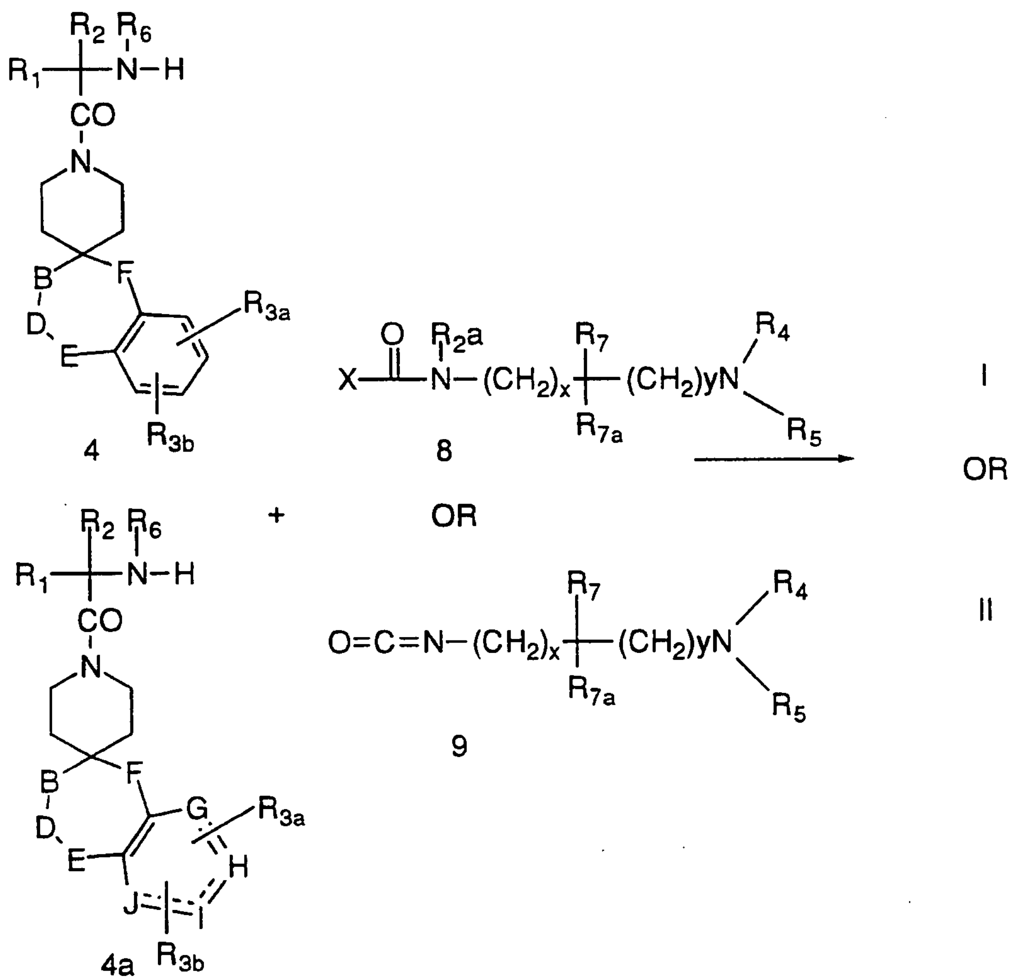
SCHEME 4



Compounds of formula **I** and **II**, wherein A is N(R2)-(CH2)z-C(R7)(R7a)-(CH2)y, can be prepared as shown in Scheme 5 by reacting **4** or **4a** with reagents **8**, wherein X is a good leaving group such as Cl, Br, I, imidazole. Alternatively, **4** and **4a** can be reacted with an isocyanate of formula **9** in an inert solvent such as 1,2-dichloroethane. If R_4 or R_5 is hydrogen in the final product, the

reagents 8 and 9 will bear a removable protecting group L in place of R_4 or R_5.

SCHEME 5



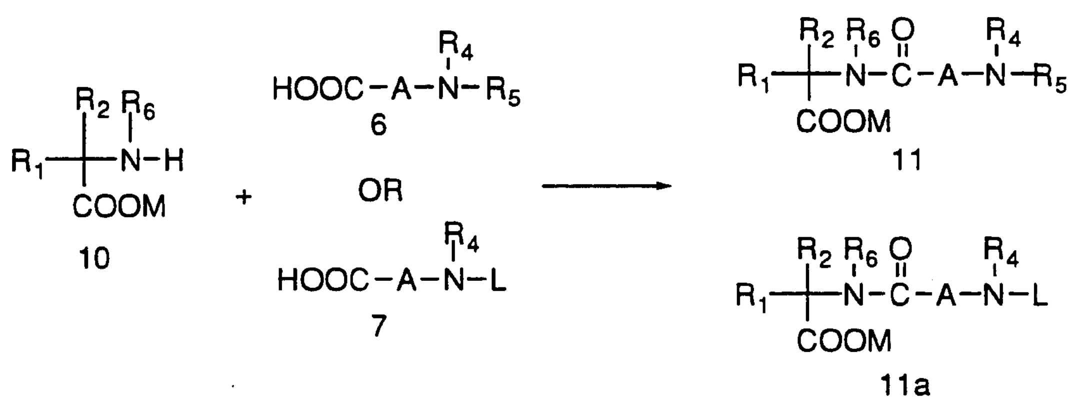
The compounds I and **II** of the present invention can also be prepared in a convergent manner as described in reaction schemes 6, 7 and 8.

The protected amino acid derivatives **10** are, in many cases, commercially available where M = methyl, ethyl, or benzyl esters. Other ester protected amino acids can be prepared by classical methods familiar to those skilled in the art. Some of these methods include the reaction of a protected amino acid with a diazoalkane and removal of a protecting group L, the reaction of an amino acid with an

appropriate alcohol in the presence a strong acid like hydrochloric acid or p-toluenesulfonic acid. Synthetic routes for the preparation of new amino acids are described in Schemes 14, 15, and 16.

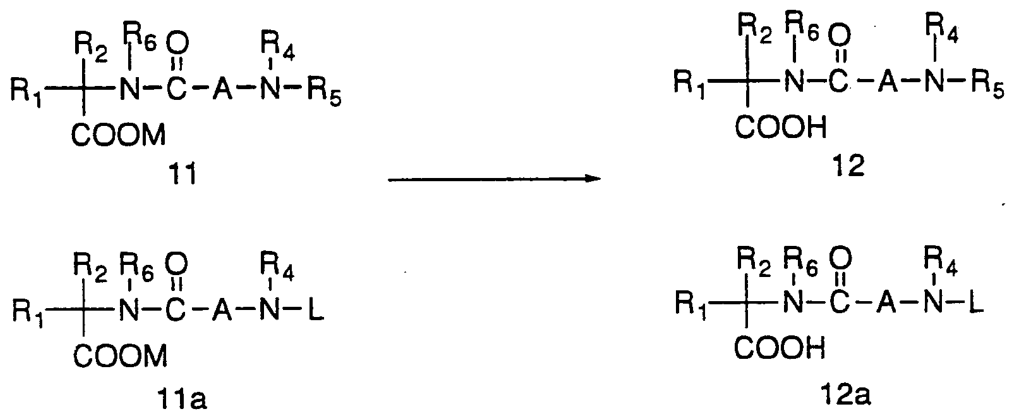
Intermediates of formula **11** and **11a**, can be prepared as shown in Scheme 6 by coupling of amines **10** to amino acids **6** and/or **7**, wherein L is a protecting group, as described above in Scheme 3. When a urea linkage is present in **11** or **11a**, it can be introduced as illustrated in Scheme 5.

SCHEME 6



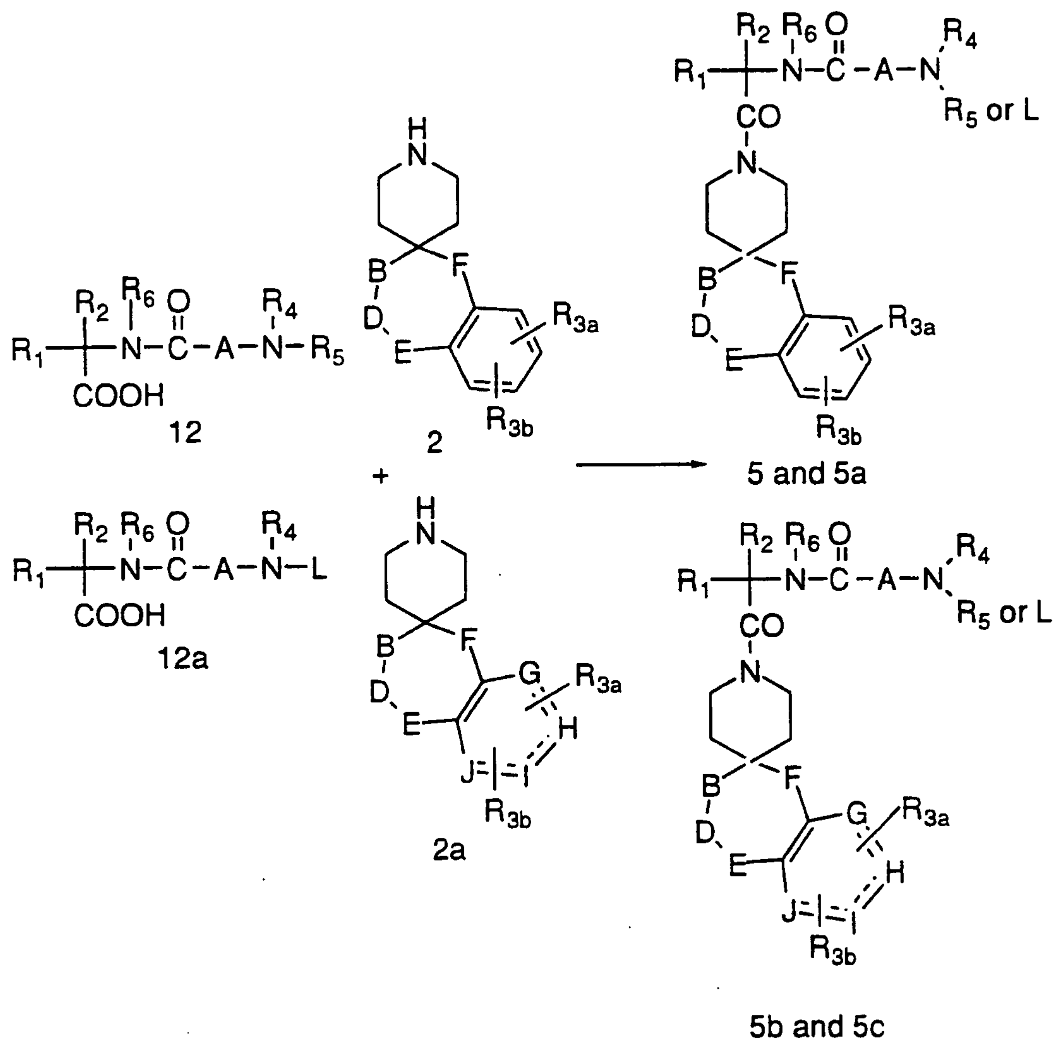
Conversion of the ester **11** or **11a** to intermediate acids **12** or **12a** can be achieved by a number of methods known in the art as described in Scheme 7; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent like aqueous methanol. In addition, removal of benzyl group can be accomplished by a number of reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent such as methanol. An allyl ester can be cleaved with tetrakis-triphenylphosphine palladium catalyst in the presence of 2-ethylhexanoic acid in a variety of solvents including ethyl acetate and dichloromethane (see *J. Org. Chem.* **1982**, *42*, 587).

SCHEME 7



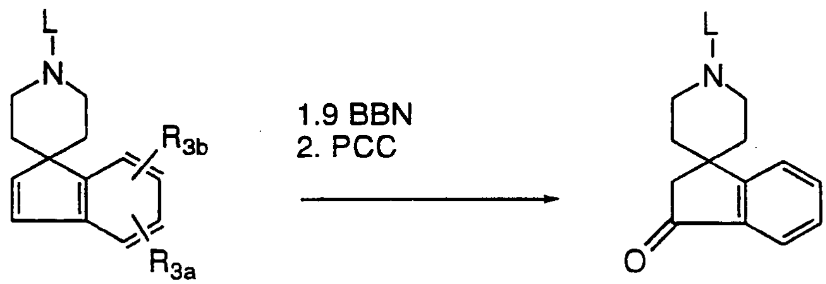
Acid **12** or **12a** can then be elaborated to **5** & **5a** and **5b** & **5c** as described in Scheme 8. Coupling of spiro piperidines of formula **2** and **2a** to acids of formula **12** or **12a**, wherein L is a suitable protecting group, is conveniently carried out in an inert solvent such as dichloromethane by a coupling reagent such as dicylohexyl carbodiimide (DCC) or EDC in the presence of 1-hydroxybenztriazole (HOBT). Alternatively, the coupling can also be effected with a coupling reagent such as benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate ("BOP") in an inert solvent such as dichloromethane. Transformation of **5a** & **5c** to **I** and **II** is achieved by removal of the protecting group L. When R4 and/or R5 is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 4.

SCHEME 8



The preparation of oxygenated spiroindanyl piperidine intermediates is illustrated in scheme 9 in which R3a and R3b are both hydrogens. Hydroboration of the protected spiroindene **13** followed by oxidative workup with pyridinium chlorochromate provides the spiroindanone **14** .

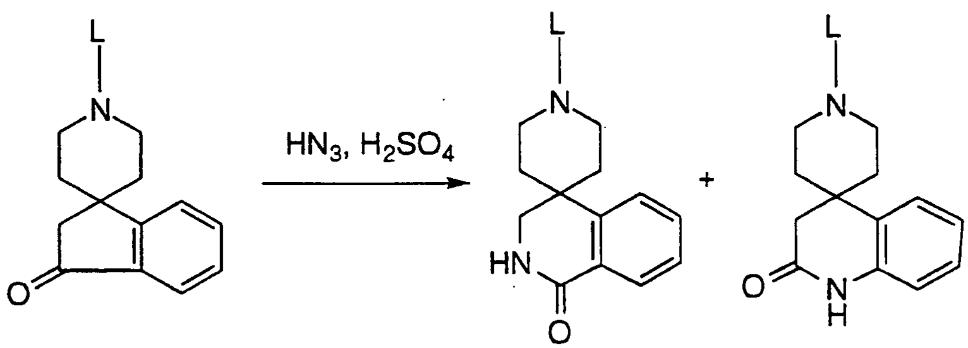
SCHEME 9



13 14

Conversion of spiroindanes into benzolactam intermediates is illustrated in Scheme 10. The treatment of the spiroindanone with hydrazoic acid in an inert solvent such as chloroform (Schmidt reaction) is one of the many suitable literature methods for this transformation. A mixture of two benzolactams is formed in this example. The isomers are easily separated by chromatography on silica gel. These intermediates can then be deprotected and incorporated into growth hormone secretagogues as depicted in Schemes 1 and 8 utilizing generic intermediate **2**.

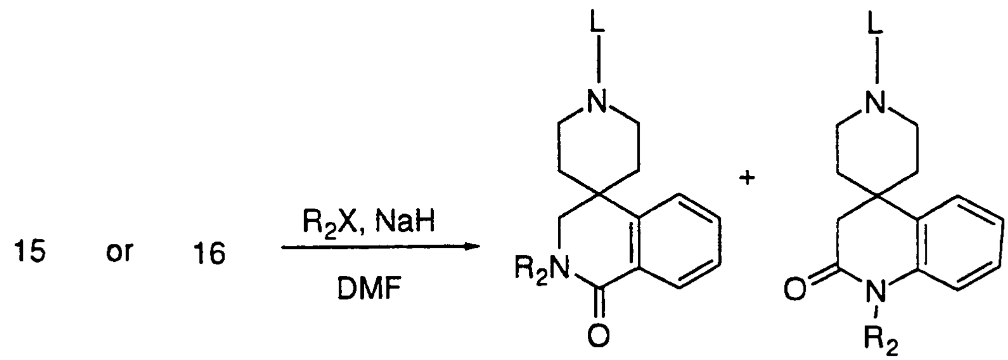
SCHEME 10



14 15 16

Alkylation of **15** and **16** with an alkyl halide in a solvent such as DMF in the presence of NaH afford **17** and **18** ($R_2 = C_1$-C_4 alkyl).

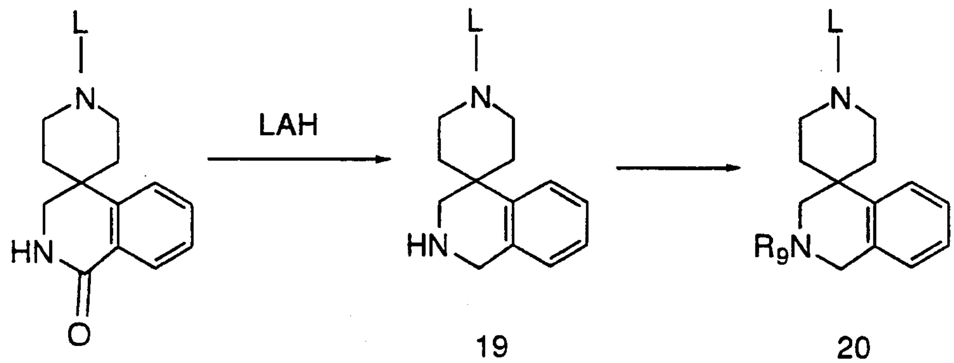
SCHEME 10A



17 18

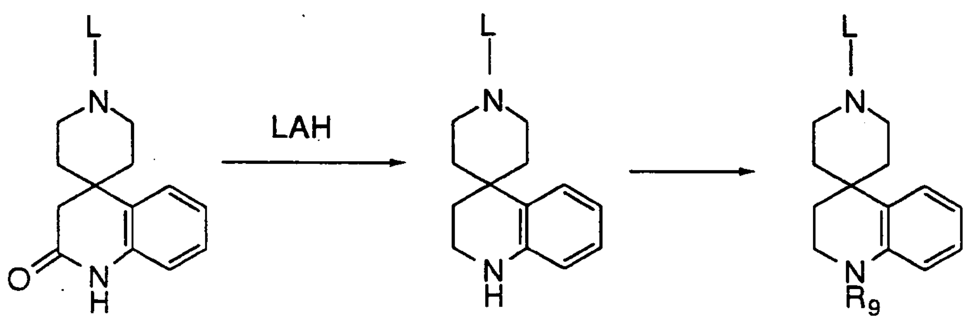
When L is an appropiate protecting group such as a benzyl group the amides can be reduced with lithium aluminum hydride to provide the amines **19** and **21**. These amines where R_2=H can then be alkylated, arylated, acylated, or reacted with substituted sulfonyl halides or isocyanates employing conditions known to those skilled in the art to afford compounds **20** and **22**. Removal of the protecting group (L) by hydrogenolysis using a palladium catalyst provides intermediates that can be incorporated into the secretagogues of this invention using the chemistry illustrated in Schemes 1 and 8 shown above which utilize generic intermediate **2**.

SCHEME 11



15 19 20

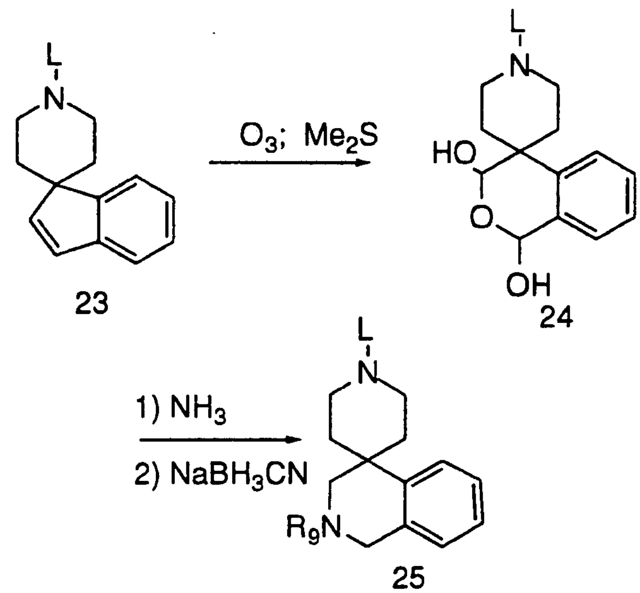
SCHEME 11A



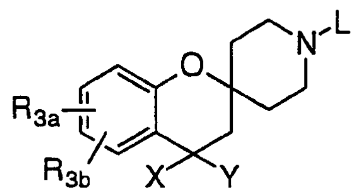
16 21 22

Alternatively, the 1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidine] ring system can be prepared as outlined in Scheme 12. The ozonolysis of the protected spiroindene followed by dimethyl sulfide treatment gives a hemiacetal intermediate 24 which under reductive amination and acylation conditions provides amine 25. The amino protecting group (L) has been defined above.

SCHEME 12

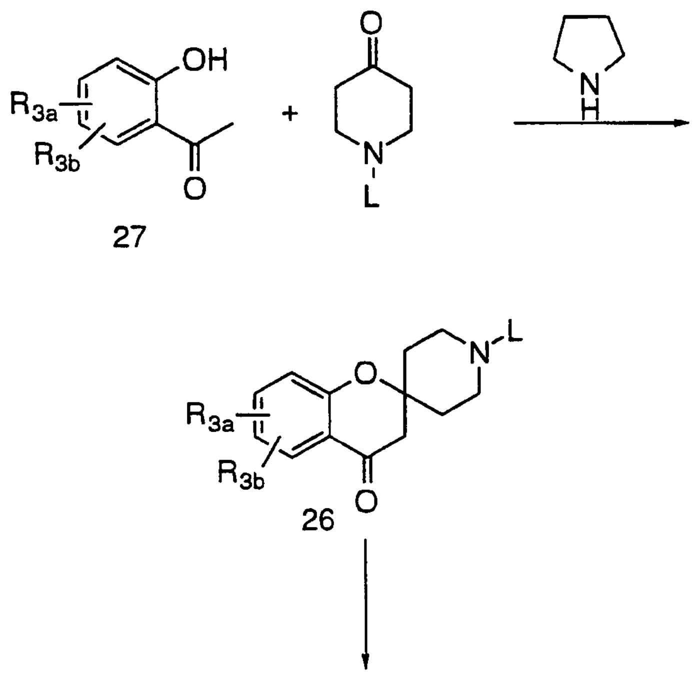


The ring analogs of formula 26, where X, Y is H,H; OH,H; H,OH; and =O may be prepared by methods described in the literature and known to those skilled in the art. For example, as illustrated in Scheme 13, the spiro[2H-1-benzopyran-2,4'-piperidine] analog can be prepared from a substituted or unsubstituted 2-hydroxyacetophenone and a properly protected 4-piperidone as described by Kabbe, H. J. Synthesis 1978, 886-887 and references cited therein. The 2-hydroxyacetophenones, in turn, are either commercially available or can be prepared by routes in the literature known to those skilled in the art. Such methods are described by Chang, C. T. et al, in J. Am. Chem. Soc., 1961, 3414-3417. and by Elliott, J. M. et al, in J. Med. Chem. 1992, 35, 3973-3976. Removal of the protecting group as described in: Protective Groups in Organic Synthesis, Greene, T. W., Wuts, P. G., John Wiley & sons, New York, 1991, and Olofson, R.A. et al, J. Org. Chem. 1984, 49, 2081-2082, provides the amine which then can be incorporated into a growth hormone secretagogue via the chemistry detailed in Schemes 1 and 8 shown above which utilize generic intermediate 2.



26

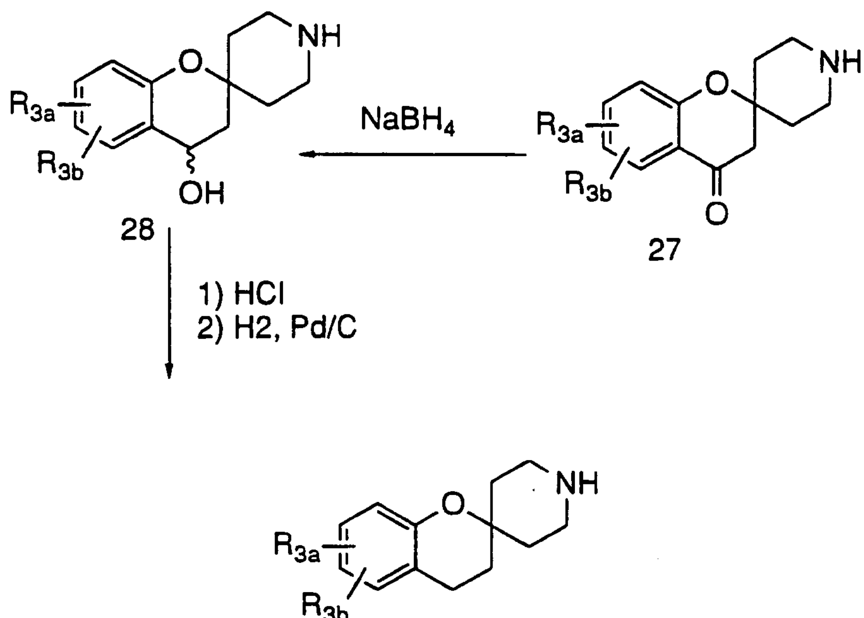
SCHEME 13



27

26

SCHEME 13 (CONT'D)

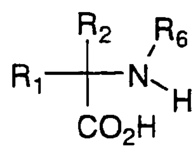


The ketone functionality in compounds of general structure 27 may be reduced to an alcohol using sodium borohydride or may be fully reduced to a methylene also employing conditions known to those skilled in the art. For example, reduction of the ketone with sodium borohydride, followed by treatment with concentrated hydrochloric acid and hydrogenation yield compounds with general structure 29. The amine of structure 27, 28, or 29 can then be incorporated into a growth hormone secretagogue via the chemistry detailed in Schemes 1 and 8 utilizing generic formula **2**. Alternatively, the ketone can often be reduced after incorporation into the compounds of Formula I.

Preparation of chiral hydroxyspiro[2H-1-benzopyran-2,4'-piperidine] analogs can be achieved using optically active reducing agents and the crystallization of diastereomeric salts.

The compounds of formulas I and II of the present invention are prepared from a variety of substituted natural and unnatural amino acids such as those of formulas **30** and **6** and **7** where A is $-(CH_2)_x-C(R_7)(R_{7a})-(CH_2)_y-$. The preparation of many of these acids has been described in the US patent 5206237.

The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art (Williams, R. M. "*Synthesis of Optically Active α-Amino Acids*" Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-



30

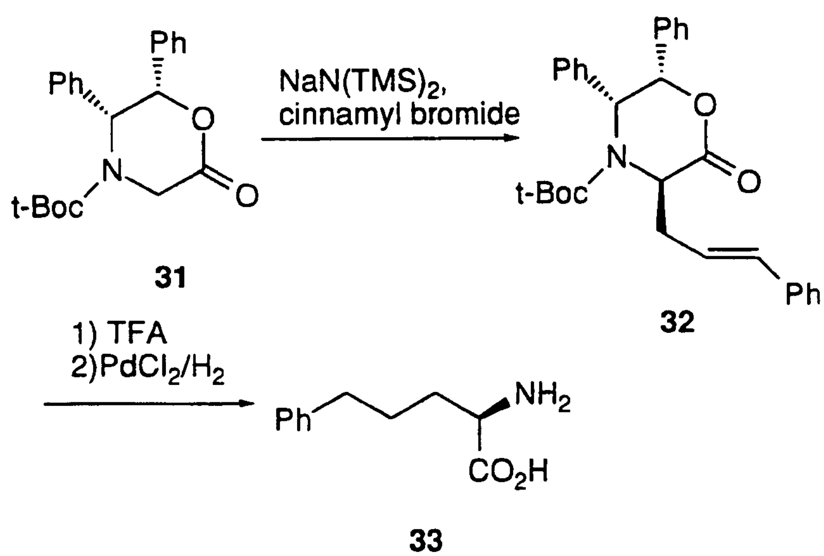
amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates can be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates can be converted to a mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in *J. Am. Chem. Soc.* **1989**, *111*, 6354-6364.

When it is desirable to synthesize these intermediates in optically pure form, some established methods include: (1) asymmetric electrophilic amination of chiral enolates (*J. Am. Chem. Soc.* **1986**, *108*, 6394-6395, 6395-6397, and 6397-6399), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (*J. Am. Chem. Soc.* **1992**, *114*, 1906; *Tetrahedron Lett.* **1987**, *28*, 32), (3) diastereoselective alkylation of chiral glycine enolate synthons (*J. Am. Chem. Soc.* **1991**, *113*, 9276; *J. Org. Chem.* **1989**, *54*, 3916), (4) diastereoselective nucleophilic addition to a chiral electrophilic glycinate synthon (*J. Am. Chem. Soc.* **1986**, *108*, 1103), (5) asymmetric

hydrogenation of prochiral dehydroamino acid derivatives ("*Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D., Ed; Academic Press: Orlando, FL, 1985; Vol 5), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.* **1978,** *17*, 176).

For example, alkylation of the enolate of diphenyloxazinone **31** (*J. Am. Chem. Soc.* **1991,** *113*, 9276) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford **32** which is converted into the desired (D)-2-amino-5-phenylpentanoic acid **33** by removing the N-t-butyloxycarbonyl group with trifluoroacetic acid and hydrogenation over a $PdCl_2$ catalyst (Scheme 14)

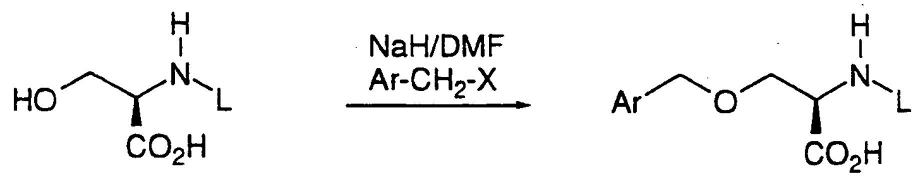
SCHEME 14



Intermediates of formula **30** which are O-benzyl-(D)-serine derivatives **34** are conveniently prepared from suitably substituted benzyl halides and N-protected-(D)-serine **34**. The protecting group L is conveniently a BOC or a CBZ group. Benzylation of **34** can be achieved by a number of methods well known in the literature including deprotonation with two equivalents of sodium hydride in an inert solvent such as DMF followed by treatment with one

equivalent of a variety of benzyl halides (*Synthesis* **1989**, 36) as shown in Scheme 15.

SCHEME 15

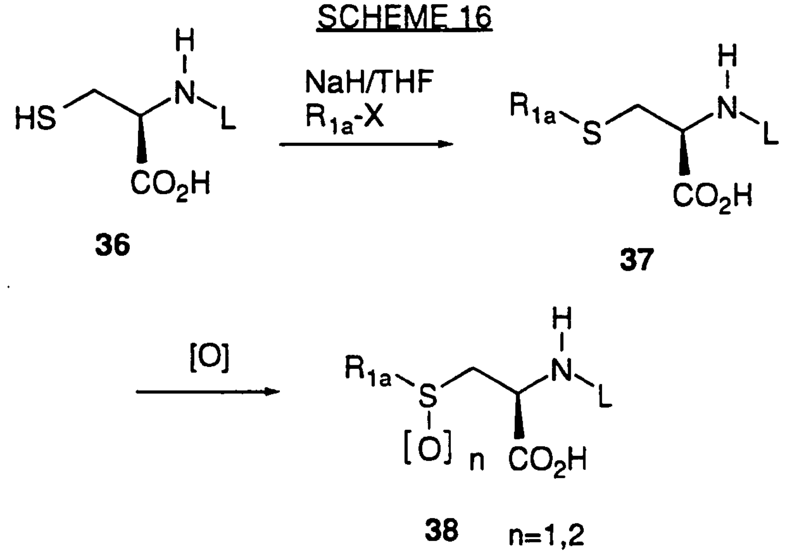


34 **35**

The O-alkyl-(D)-serine derivatives are also prepared using the alkylation protocol shown in Scheme 15. Other methods that could be utilized to prepare (D)-serine derivatives of formula **35** include the acid catalyzed benzylation of carboxyl protected intermediates derived from **34** with reagents of formula $ArCH_2OC(=NH)CCl_3$ (O. Yonemitsu et al. *Chem. Pharm. Bull.* **1988**, *36*, 4244). Alternatively, alkylation of the chiral gylcine enolates (*J. Am. Chem. Soc.* **1991**, *113*, 9276; *J. Org. Chem.* **1989**, *54*, 3916) with $ArCH_2OCH_2X$ where X is a leaving group affords 35. In addition D,L-O-aryl(alkyl)serines can be prepared and resolved by methods described above.

The alkylation of N-protected-(D)-cysteine **36** is carried out by the procedure described in the (D)-serine derivative synthesis and illustrated below with R_{1a}-X where X is a leaving group such as halides and mesyloxy groups as shown in Scheme 16.

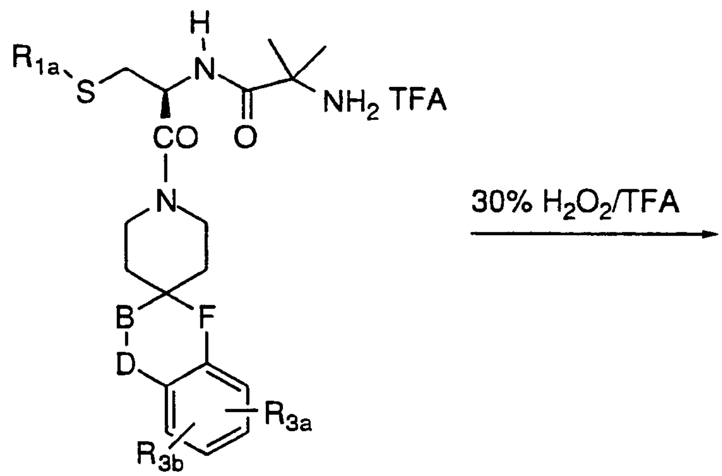
SCHEME 16



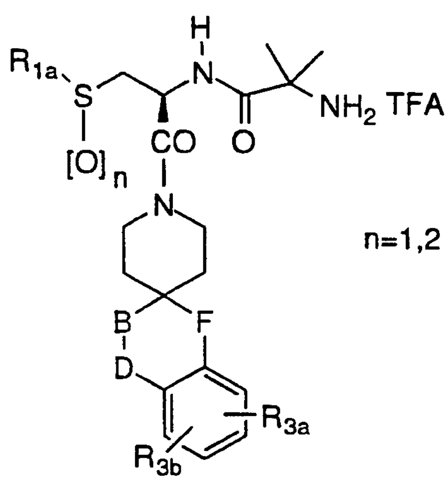
The oxidation of the cysteine derivatives **37** to the sulfoxide **38** (n=1) and the sulfone **38** (n=2) can be accomplished with many oxidizing agents. (For a review of the oxidation of sulfides see *Org. Prep. Proced. Int.* **1982,** *14*, 45.) Sodium periodate (*J. Org. Chem.* **1967**, *32*, 3191) is often used for the synthesis of sulfoxides and potassium hydrogen persulfate (OXONE) (*Tetrahedron Lett.* **1981**, *22*, 1287) is used for the synthesis of sulfones.

Hence, a variety of substituted amino acids may be incorporated into a growth hormone secretagogue via the chemistry detailed in Schemes 1 and 8. The secretagogues that contain a sulfoxide or a sulfone functional group can also be prepared from the cysteine secretagogues by using sodium periodate or OXONE®. Alternatively hydrogen peroxide may be used as the oxidizing reagent in the last step of the synthesis as shown in Scheme 17. The sulfoxide **40** (n=1) and sulfone **40** (n=2) analogs can be separated by preparative thin layer chromatography.

SCHEME 17



39



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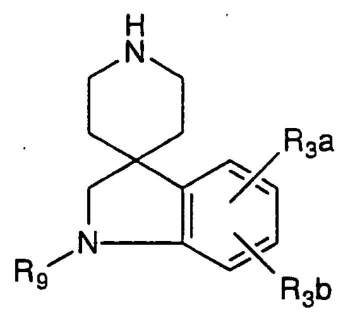
Removal of amino protecting groups can be achieved by a number of methods known in the art; as described above and in Protective Groups in Organic Synthesis T.W. Greene, John Wiley and Sons, NY. 1981.

Compounds of formula I wherein R^4 and R^5 are each hydrogen can be further elaborated by reductive alkylation with an aldehyde by the aforementioned procedures or by alkylations such as by reaction with various epoxides. The products, obtained as

hydrochloride or trifluoroacetate salts, are conveniently purified by reverse phase high performance liquid chromatogrphy (HPLC) or by recrystallization.

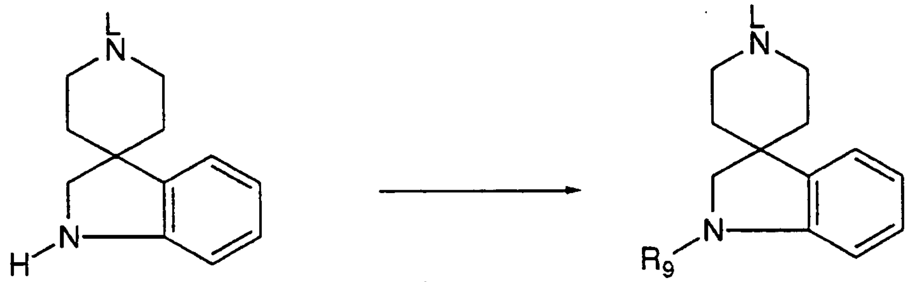
The spiro piperidines of formula **41** can be prepared by a number of methods, including the syntheses as described below.



41

The spiropiperidines of formula **42**, wherein L is a defined protecting group, can be synthesized by methods that are known in the literature (for example H. Ong et al *J. Med. Chem.* **1983**, *23*, 981-986). The indoline nitrogen of **42**, wherein L is a protecting group such as methyl or benzyl, can be reacted by with a variety of electrophiles to yield spiro piperidines of formula **43**, wherein R9 can be a variety of functionalities. Compound **42** can be reacted with, for example, isocyanates in an inert solvent like dichloromethane to yield urea derivatives, chloroformates in an inert solvent like dichloromethane to yield carbamates, acid chlorides,

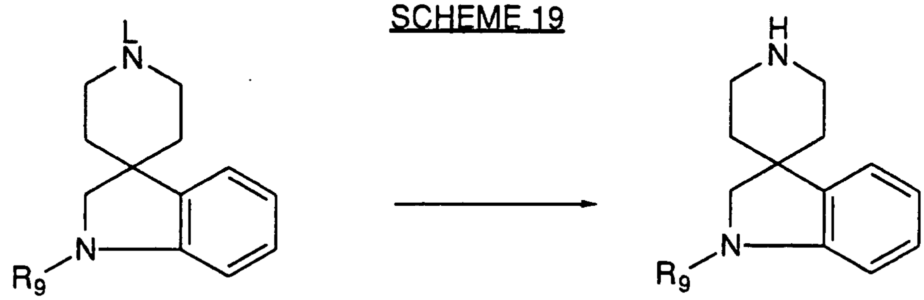
SCHEME 18



42 43

anhydrides, or acyl imidazoles to generate amides, sulfonyl chlorides to generate sulfonamides, sulfamyl chlorides to yield sulfamides. Also, the indoline nitrogen of **42** can be reductively alkylated with aldehydes with conditions known in the art. When the aldehyde used in the reductive amination reaction is a protected glyoxylic acid of structure HCOCOOM, wherein M is a defined protecting group, M can be removed from the product and further derivatized. Alternatively, **42** can be reacted with epoxides to produce **43**, wherein R9 is β-hydroxy-substituted alkyl or arylalkyl groups. The indoline **42** can also be transformed to compounds of formula **43**, wherein R9 = phenyl or substituted phenyl, heteroaryl or substituted heteroaryl, by carrying out the reacting **42** with a fluoro phenyl or fluoro heteroaryl reagent. This chemistry is detailed in H. Ong et al *J. Med. Chem.* **1983**, *23*, 981-986.

SCHEME 19

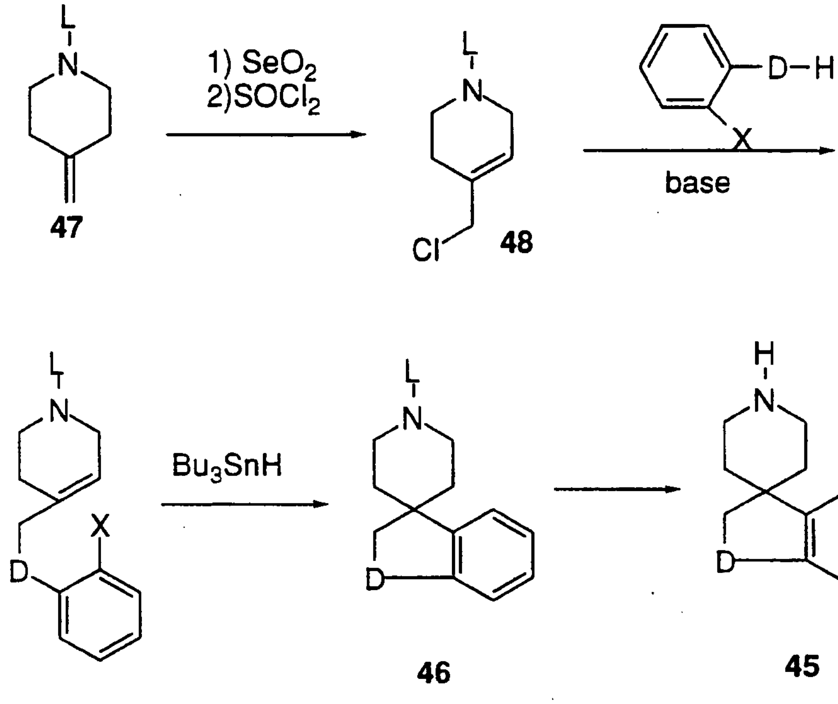


43 44

The spiro piperidine intermediate **43** (L = Me or Bn), wherein R9 is hydrogen or most of the derivatives described above, can be demethylated or debenzylated to produce **44**, wherein R9 is hydrogen or most of the derivatives described above, as shown in Scheme 19. For compounds of formula **43**, wherein L = Me, demethylation can be carried out by a number methods familiar those skilled in the art. For example, demethylation of **43** be accomplished by reacting it with cyanogen bromide and potassium carbonate in an inert solvent solvent such as dichloromethane to yield a cyanamide which can reduced to give **44** by treatment with lithium aluminum hydride in refluxing tetrahydrofuran, refluxing strong acid like aqueous hydrochloric acid, or with Grignard reagents like methyl magnesium bromide. Alternatively, demethylation of **43** can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* **1984**, *49*, 2795 and references therein. For intermediates of formula **43**, wherein L = Bn, removal of benzyl group can be accomplished by reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent like methanol. Alternatively, debenzylation of **43**, L = Bn, can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* **1984**

The spiro heterocyclic compounds **45** can be prepared by a number of methods, including the syntheses as described in Scheme 20.

SCHEME 20

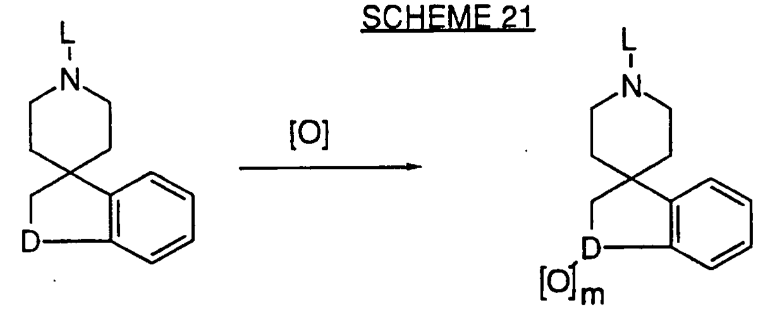


D=O, S, NR9, X=halides, Se, S

Allylic oxidation of the protected piperidine **47** is accomplished by classical methods familiar to those skilled in the art (Rabjohn, N. *Org. React.* **1976**, *24*, 261). The resulting allylic alcohol is treated with thionyl chloride in an inert solvent such as benzene to provide the corresponding chloride **48**. When D=O or S, the alkylation is carried out in DMF or acetone as solvent with potassium carbonate as a base, and when D=NR9 (R9=H, alkyl, aryl, acyl, sulfonyl, carbamate) the reaction is carried out with sodium hydride as a base in an inert solvent such as THF to afford the cyclization precursor **49**. When L is a defined protecting group, compound **49** can be cyclized by a number methods familiar to those skilled in the art. For example, cyclization of **49** can be accomplished by reaction with tributyltin hydride (Curran , D. P. *Synthesis* **1988**, 417 and 489) in an inert solvent such as benzene to yield **46**. Alternatively, compound **46** (D=NR9) can be prepared by the method shown in Schemes 18 and 19. When D=S, compound **46** can be oxidized to the sulfoxide **47** (n=1) and the sulfone **47** (n=2) by many

oxidizing agents (Scheme 21). For example, sodium periodate is often used for the synthesis of sulfoxides and OXONE is used for the synthesis of sulfones. Removal of the protecting group provides the amine **45** which then can be incorporated into a growth hormone secretagogue via the chemistry detaileds in Scheme 1 and 8 shown above which utilize generic intermediate **2.**

SCHEME 21



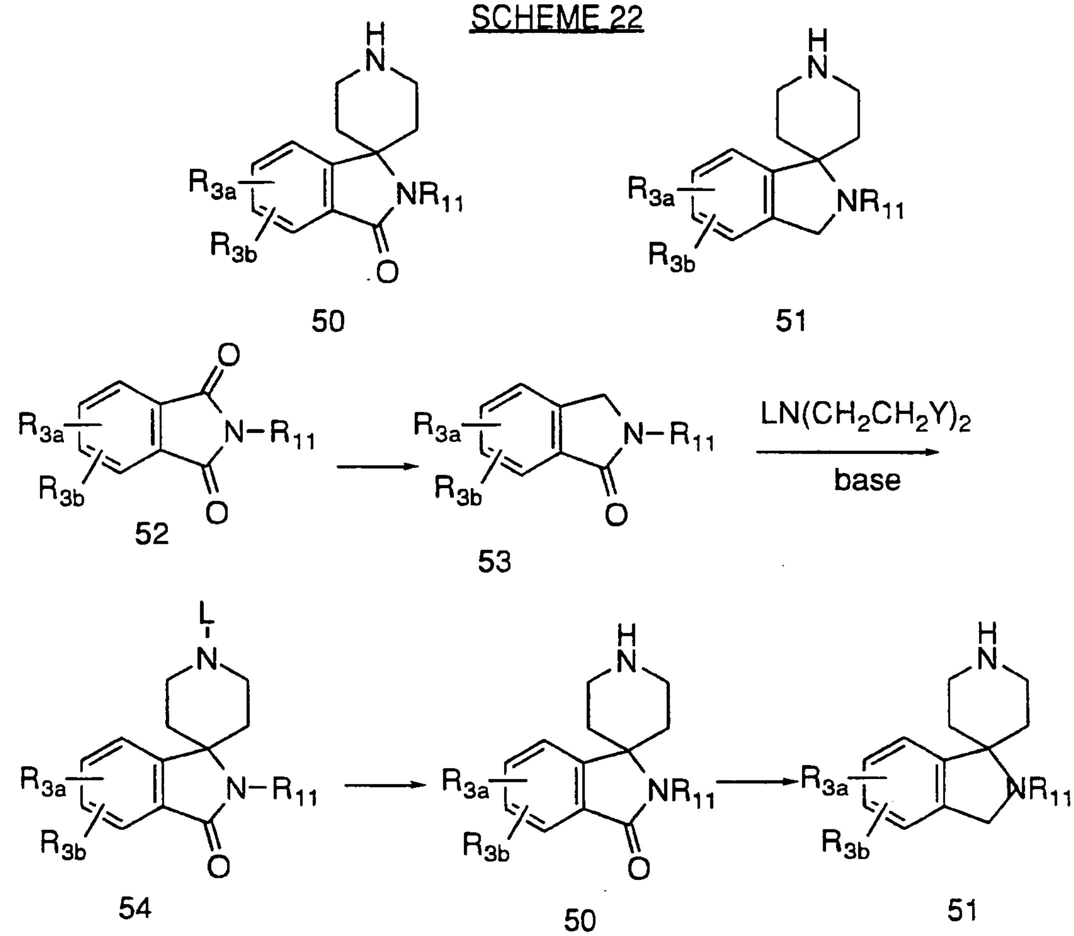
46 D=S

46 D = S(O)$_m$ m=1,2

The spiro piperidines of formula **50** and formula **51** can be prepared by the syntheses described in Scheme 22.

The phthalimidines of formula **53**, where R_{11} is defined as alkyl, aryl, (CH2)$_q$-aryl, or a protecting group, are either commercially available or can be synthesized from the corresponding phthalimides by methods that are known in the literature (for example, Bewster et al in *J. Org. Chem.*, 1963, <u>28</u>, 501; Mcalees *et al J. Chem. Soc.*, 1977, 2038). The phthalimidine **53** can be alkylated in the presence of a base, such as potassium hydride, lithium or potassium bis(trimethylsilyl)amide, with the protected bis 2-haloethyl amine, where L is a defined protecting group such as methyl, benzyl, t-BOC, or CBZ, etc., and Y could be Cl, Br, I, to yield the spiropiperidine **54**. The protecting group could be removed by procedures described above to yield formula **50**. Reduction of the lactam in formula **50** by hydrides, such as lithium aluminum hydride, yields formula **51**.

SCHEME 22



It is noted that the order of carrying out the foregoing reaction schemes is not significant and it is within the skill of one skilled in the art to vary the order of reactions to facilitate the reaction or to avoid unwanted reaction products.

The growth hormone releasing compounds of Formula I and II are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release. Other

hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neurokinins; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formulas I and II can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I and II can be administered to animals, including man, to release growth hormone *in vivo*. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I and II can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I and II in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an

anabolic agent in addition to at least one of the compounds of Formula I and II or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the catabolic side effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, estrogens, β-agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the growth hormone secretagogues of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and the newly discovered GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or α- adrenergic aginists such as clonidine or serotonin 5HTID agonists such as sumitriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; prevention of catabolic side effects of glucocorticoids, treatment of osteoporosis, stimulation of the

immune system, acceleration of wound healing, accelerating bone fracture repair, treatment of growth retardation, treating acute or chronic renal failure or insufficiency, treatment of physiological short stature, including growth hormone deficient children, treating short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacement of growth hormone in stressed patients; treatment of osteochondrodysplasias, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; attenuation of protein catabolic response after a major operation; treating malabsorption syndromes, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; to stimulate thymic development and prevent the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and cartilage growth; treatment of neurological diseases such as peripheral and drug induced neuropathy, Guillian-Barre Syndrome, amyotrophic lateral sclerosis, multiple sclerosis, cerebrovascular accidents and demyelinating diseases; stimulation of the immune system in companion animals and treatment of disorders

of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep.

It will be known to those skilled in the art that there are numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with the growth hormone secretagogues of this invention will bring additional, complementary, and often synergistic properties to enhance the growth promotant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic Bone Diseases. *Trends in Endocrinol. Metab.*, 1993, *4*, 19-25. Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl - APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995. According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1

N-[1(R)-[(2',3'-dihydro-2-oxo,spiro[piperidine-4,4'(1H)-quinolin]-1'yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: 1'-(t-butyloxycarbonyl)3,4-dihydro-3-oxospiro[1H-indene-1,4'-piperidine]

To a solution of 661 mg (2.31 mmol) of 1'-(t-butyloxycarbonyl)spiro[1H-indene-1,4'-piperidine] [prepared by the method of Chambers, et al, J. Med. Chem., 1992, 35, 2036] in 5.0 ml of THF was added 5.8 ml (1.0 M THF, 2.9 mmol) of 9-BBN. The reaction mixture was heated at 70°C until TLC analysis indicated that the starting material was consumed. The solution was concentrated and the residue was dissolved in dichloromethane. The solution was cooled to 0°C and 4.1 g (19.2 mmol) of PCC was added slowly over 15 minutes. The reaction mixture was warmed to room temperature and then to reflux for 30 minutes. The solution was then diluted with ether and filtered through a pad of a mixture of celite and florisil. Purification by flash chromotgraphy (silica gel, hexane/ethyl acetate, 4:1) gave 326 mg (47%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$): 7.75-7.60 (m, 2 H), 7.50-7.44 (m, 2 H), 4.30-4.15 (m, 2 H), 2.85 (dt, 2 H), 2.63 (s, 2 H), 1.98 (dt, 2 H), 1.53-1.40 (m, 2 H), 1.49 (s, 9 H).

Step B: Spiro[1H-indene-1,4'-piperidin]-3(2H)-one trifluoroacetamide

A solution of the intermediate from Step A in a 1:1:0.5 mixture of trifluoroacetic acid, dichloromethane and anisole was stirred for 1 hour and then concentrated and azeotroped from toluene to give the title compound.

^{1}H NMR (200 MHz, $CDCl_3$): 7.81-7.70 (m,1 H), 7.62-7.45 (m, 2 H), 7.22-7.15 (m, 1 H), 3.72-3.58 (m,2 H), 3.29-3.04 (m, 2 H), 2.70 (s, 2 H), 2.47 (dt, 2 H), 1.85-1.75 (m, 2 H).

Step C: Trifluoroacetamide-2,3-dihydrospiro[indene-1,4'piperidine]

To a solution of 1.0 g (3.21 mmol) of the intermediate obtained in Step B in 3.0 ml of dichloromethane was added 0.945 ml (6.74 mmol) of triethylamine and 50 mg of DMAP and finally 0.501 ml (3.53 mmol) of trifluroacetic acid anhydride. The reaction mixture was stirred for 3 hours and then diluted with 20 ml of dichloromethane. The solution was washed with water, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (silica gel, hexane/ethyl acetate 2:1) gave 568 mg (1.91 mmol).
^{1}H NMR (200 MHz, $CDCl_3$): 7.79-7.64 (m, 2 H), 7.52-7.41 (m, 2 H), 4.75-4.65 (m,1 H), 4.22 -4.08 (m, 1 H), 3.37 (dt, 1 H), 2.92 (dt, 1 H), 2.70 (s, 2 H), 2.08 (dt, 2 H), 1.71-1.62 (m, 2 H) .

Step D: Triflouroacetamide-3',4'-dihydro-2-oxospiro[piperidine-4,4'(1H)-quinoline]

To a solution of 218 mg (3.36 mmol) of sodium azide in 0.285 ml of water and 1.5 ml of chloroform at 0°C was added 0.105 ml of sulfuric acid. The reaction mixture was stirred for 2.5 hours and then the layers were separated and the chloroform layer was dried over sodium sulfate. The hydrazic acid solution was then added to a solution of 400 mg (1.34 mmol) of the intermediate obtained from Step A. To this solution was added 0.400 ml of sulfuric acid over 5 minutes. The reaction mixture was stirred for 20 minutes and then for 45 minutes at 45°C and finally for 16 hours at room temperature. The sulfuric acid layer was added to ice and then made basic with 50% sodium hydroxide. The aqueous layer was extracted with ethyl acetate. The ethyl acetate extracts were dried over sodium sulfate and concentrated. Purification of a 100 mg portion of the crude product by flash chromatography (silica gel, dichloromethane/ethyl acetate 1:1 followed by 1:2) gave 50 mg (0.160 mmol) of a high RF material and 16 mg (0.051 mmol) of a low RF material.

^{1}H NMR (200 MHz, $CDCl_3$, high RF): 8.9-8.7 (bs, 1 H), 7.40-7.21 (m, 2 H), 7.18-7.04 (m, 1 H), 6.90-6.86 (m, 1 H), 4.52-4.36 (m, 1 H), 3.97-3.83 (m, 1 H), 3.52 (dt, 1 H), 3.22 (dt, 1 H), 2.79 (s, 2 H), 2.12-1.66 (m, 4 H). ^{1}HNMR (200 MHz, $CDCl_3$, low RF): 8.12(dd, 1 H), 7.60-7.52 (m, 1 H), 7.45-7.35 (m, 2 H),6.95 (bs, 1 H), 4.56-443 (m,1 H), 4.03-3.96 (m,1 H),3.64-3.62 (m,2 H), 3.49-3.35 (m, 1 H), 3.11 (dt,1 H), 2.20-1.80 (m, 4 H).

Step E: 3',4'-dihydro-2-oxospiro[piperidine-4,4'(1H)-quinoline]

A solution of 49 mg (0.157 mmol) of the high RF material from Step B in methanol/water 4:1 with excess potasium hydroxide was stirred over night. The solution was concentrated and water and ethyl acetate were added to the residue. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated.to give 31 mg (0.143 mmol) of the title compound.

Step F: N-[1(R)-[(2',3'-dihydro-2-oxo,spiro[piperidine-4,4'(1H)-quinolin]-1'yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[1,1-dimethylethyloxycarbonyl]amino]-2-methylpropanamide

To a solution of 29 mg (0.134 mmol) of the intermediate obtained in Step C, 65 mg (0.167 mmol) of 2-amino-N-[1(R)-[2',3'-dihydro-2-oxospiro[piperidine-4,4'(1'H)-quinolin]-1-yl)carbonyl]-2-(1H-indol-3-yl)ethyl-2-methylpropanamide, and 24 mg (0.174 mmol) of HOBT in dichloromethane was added 33 mg (0.174 mmol) of EDC. The reaction was stirred overnight and then worked up and purified as described for Example 1 (Step A) with one exception, dichoromethane/ acetone was used for the chromatography. 34.8 mg (0.059 mmol) of the title compound was obtained.

Step G: N-[1(R)-[(2',3'-dihydro-2-oxo,spiro[piperidine-4,4'(1H)-quinolin]-1'yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

The title compound (7.2 mg, 0.013 mmol) was obtained from the intermediate from Step D (14 mg, 0.023 mmol) according to the procedure described for Example 1 (Step C) with one exception. The hydrochloride salt was generated from the purified free amine by the addition of 4 N HCl in dioxane in this case.
^{1}H NMR (400 MHz, CD_3OD, 2:1 mixture of rotomers): 8.34 (d, 2/3 H), 8.27 (d, 1/3 H), 7.59 (d, 2/3 H), 7.55 (d, 1/3 H), 7.38 (d, 1/3 H), 7.33 (d, 2/3 H), 7.25 (d, 1/3 H), 7.18-6.98 (m, 4 H), 6.85 (d, 1/3 H), 6.80 (d, 2/3 H), 6.68 (d, 2/3 H), 5.23-5.17 (m, 1 H), 4.22-4.19 (m, 2/3 H), 4.09-3.95 (m, 1/3 H), 3.62-3.59 (m, 1/3 H), 3.36-3.17 (m, 2 2/3 H), 3.08 (dt, 1/3 H), 2.75 (dt, 1/3 H), 2.69 (dt, 2/3 H), 2.48 (dd, 2 H), 1.93-1.75 (m, 2/3 H), 1.60 (s, 3 H), 1.58 (s, 2 H), 1.40-1.32 (m, 1 H), 1.51 (s, 1 H), 1.10 (m, 1/3 H), 1.02 (m, 2/3 H), 0.90 (dt, 2/3 H), 0.22 (dt, 2/3 H). FAB-MS: m/e 490 (m+1).

EXAMPLE 2

N-[1(R)-[(2',3'-dihydro-1-oxospiro[piperidine-4,4'(1H)-isoquinolin]-1'yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: [3',4'-dihydro-1-oxospiro[piperidine-4,4'(1H)-isoquinoline]

The title compound (11.3 mg, 0.036 mmol) was prepared from the low RF intermediate from Example 1 (Step D) (16.0 mg, 0.051 mmol) according to the procedure described for Example 13 (Step D).
^{1}HNMR (200 MHz, $CDCl_3$): 8.12 (dd, 1 H), 7.60-7.52 (m, 1 H), 7.45-7.35 (m, 2 H), 6.95 (bs, 1 H), 4.56-4.43 (m, 1 H), 4.03-3.96 (m, 1 H), 3.64-3.62 (m, 2 H), 3.49-3.35 (m, 1 H), 3.11 (dt, 1 H), 2.20-1.80 (m, 4 H).

Step B: N-[1(R)-[(2',3'-dihydro-1-oxo,spiro[piperidine-4,4'(1H)-isoquinolin]-1'yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[1,1dimethylethyloxycarbonyl]amino]-2-methyl-propanamide

The title compound (13.6 mg, 0.023 mmol) was prepared from the intermediate from Step A (10.0 mg, 0.032) and 2-amino-N-[1(R)-[2',3'-dihydro-2-oxospiro[piperidine-4,4'(1'H)-quinolin]-1-yl)carbonyl]-2-(1H-indol-3-yl)ethyl-2-methylpropanamide (21.6 mg, 0.055 mmol) according to the procedure described for Example 13 (Step D).

Step C: N-[1(R)-[(2',3'-dihydro-1-oxospiro[piperidine-4,4'(1H)-isoquinolin]-1'yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

A solution of 10.1 mg (0.017 mmol) of the intermediate obtained from Step B in 1.5 N HCl in ethyl acetate was stirred over night and then concentrated and azeotroped from methanol to yield 8.3 mg (0.015 mmol) of the title compound.
^{1}H NMR (400 MHz, CD_3OD, 2:1 mixture of rotomers): 7.94 (d, 1/3 H), 7.87 (d, 2/3 H), 7.62-7.53 (m, 2 H), 7.40-7.33 (m, 2 1/3 H), 7.18-7.10 (m, 3 H), 6.75 (d, 2/3 H), 5.22-5.18 (m, 2/3 H), 5.15 (t, 1/3 H), 4.27-4.23 (m, 2/3 H), 4.14-4.10 (m, 1/3 H), 3.68-3.61 (m, 1 H), 3.25-3.18 (m, 4 H), 3.10 (dt, 2/3 H), 2.87 (dt, 1/3 H), 2.70 (dt, 1/3 H), 2.65 (dt, 2/3 H), 1.88 (dt, 1/3 H), 1.75 (dt, 1/3 H), 1.62 + 1.61 + 1.59 + 1.51 (s, 6 H total), 1.57-1.44 (m, 1 H), 1.38-1.35 (m, 1/3 H), 1.15-1.10 (m, 1/3 H), 0.929 (dt, 2/3 H),0.19 (dt, 2/3 H). FAB-MS: m/e 490 (m+1).

EXAMPLE 3

N-[1(R)-[(4H-1-oxospiro[3H-2-benzopyran-3,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)-ethyl]-2-amino-2-methylpropanamide hydrochloride.

Step A: Spiro[3H-2-benzopyran-3,4'-piperidin]-1(4H)-one

To a suspension of 10% palladium on carbon (5 mg) in ethanol (5 mL) was added of 1'-benzylspiro[3H-2-benzopyran-3,4'-piperidine]-1(4H)-one (20 mg, 0.058 mmol). (Hashigaki et al Chem. Pharm. Bull. 32 pg 3561-3568 (1984)). Hydrogenation was performed

at 1 atmosphere pressure at room temperature. The reaction was stirred for 2 hours under hydrogen atmosphere, until TLC analysis indicated that the reaction was complete. The catalyst was removed by vacuum filtration through celite 545 and the filtrate was concentrated to give the desired product (12.4 mg, 98.5%).
FAB-MS calc. for $C_{13}H_{15}NO_2$ 217; found 218 (M+H, 100%).

Step B: N-[1(R)-[(4H-1-oxospiro[3H-2-benzopyran-3,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)-ethyl]-2-[[(1,1-dimethyl-ethyloxy)carbonyl]amino]-2-methylpropanamide

A solution of the intermediate from Step A (12 mg, 0.055 mmol) and α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid (27 mg, 0.058 mmol) in dichloromethane was cooled to 0°C and then HOBT (2 mg, 0.015 mmol), N-methyl-morpholine (8.8 mg; 0.084 mmol) and EDC (22 mg, 0.12 mmol) were added. The reaction mixture was stirred at room temperature for 1 hour, until the reaction was judged complete by TLC analysis. The solution was then washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solution was then filtered and concentrated. Purification by silica gel chromatography provided the title compound (15 mg, 47%).
FAB-MS calc. for $C_{33}H_{40}N_4O_6$ 588; Found 589 (M+H, 39%) [489 M+H-100, 42%) loss of *t*- Boc group].

Step C: N-[1(R)-[(4H-1-oxospiro[3H-2-benzopyran-3,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)-ethyl]-2-amino-2-methyl-propanamide hydrochloride

A solution of the intermediate from Step B (12 mg, 0.02 mmol) in methanol (3 mL) was cooled to 0°C. While stirring, concentrated hydrochloric acid (3 mL) was then added slowly to the mixture. The reaction was stirred for 30 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated several times from toluene. The hydrochloric salt was used without purification (10.15 mg, 96%).

^1H NMR (400 MHz, CD_3OD): The product exists as a mixture of two conformers (2:1): δ 7.977, 7.905 (2d, 2/3 H), 7.604-6.994 (m, 8 H), 5.134-5.093 (m, 1 2/3 H), Hidden 5.025-4.715 (m, 2 H), 4.191-4.114 (m, 1/3 H), 3.637-3.587 (m, 1 H), 3.344-3.299 (m, 1 H), 3.188-3.124 (m, 1 H), 3.030 (s, 2/3 H), (dt, 2.81 Hz, 9.4 Hz, 1/3 H), 2.536 (q, 1 H), 2.301 (t, 1/3 H), 1.590, 1.571 (2s, 6 H), 1.539-1.483 (m, 2/3 H), 1.275 (s, 6 H), 1.259-1.206 (m, 2/3 H), (m, 1 H), 0.633-0.545 (m, 1/3 H), -0.277 -0.361 (m, 1/3 H).

FAB-MS calc. for $C_{28}H_{32}N_4O_4$ 488; found 489 (M+H, 65%).

EXAMPLE 4

N-[1(R)-[(4',5'-dihydro-4'-oxospiro[piperidine-4,6'-[6H]thieno[2,3-b]thiopyran]-1-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-propanamide hydrochloride

Step A: N-[1(R)-[(4',5'-dihydro-4'-oxospiro[piperidine-4,6'-[6H]thieno[2,3-b]thiopyran]-1-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-propanamide

Prepared by the procedure described in Example 3, Step B. Spiro[piperidine-4,6'-[6H]thieno[2,3-b]thiopyran]-4'(5'H)-one hydrochloride, (10 mg, 0.044 mmol) EP publication 90313262.9, α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid (20 mg, 0.051 mmol), HOBT (1 eq.), N- methylmorpholine (0.01 mL, 0.093 mmol), and EDC (20 mg, 0.10 mmol). Reaction time: 5 hours. Yield: 22 mg (98%).

^1H NMR (400 MHz, $CDCl_3$): product exists as a mixture of two conformers (2:1): δ 8.240 (s, 2/3 H), 8.063 (s, 1/3 H), 7.680 (d, 2/3 H), 7.628 (d, 1/3 H), 7.416-6.962 (m, 5 H), 5.279-5.162 (m, 1 H), 4.878-4.763 (m, 1 H), 4.285 (d, 2/3 H), 3.376 (d, 2/3 H), 3.342-3.196 (m, 1 H), 3.129-2.973 (m, 1 2/3 H), 2.715-2.662 (m, 1 H), 2.285 (d, 2/3 H), 2.139 (d, 2/3 H), 1.683-1.567 (m, 8 1/3 H), 1.503, 1.454, 1.427, 1.409 (4s, 12 H), 1.278-1.217 (m, 2 H), 0.708-0.628 (m, 2/3 H).

FAB-MS calc. for $C_{31}H_{38}N_4O_5S_2$ 610; found 611 (M+H, 32%).

Step B: N-[1(R)-[(4',5'-dihydro-4'-oxospiro[piperidine-4,6'-[6H]thieno[2,3-b]thiopyran]-1-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-propanamide hydrochloride

Prepared by the procedure described in Example 15, Step C. The intermediate from previous Step (200 mg, 0.033 mmol) and methanol (3 mL). Reaction time: 1.5 hours. Yield: 12.2 mg (69%). ^{1}H NMR (400 MHz, CD_3OD): The product exists as a mixture of two conformers (2:1): δ 7.562-7.022 (m, 6 H), 5.513-5.446 (m, 6 2/3 H), 5.099-5.003 (m, 1 H), hidden 4.914-4.726 (m, 2/3 H), 4.178 (d, 1H), 3.624 (d, 1H), 3.337-3.043 (m, 2 2/3 H), 2.760-2.660 (m, 1 H), 2.324 (d, 1H), 2.234 (d, 1H), 1.597, 1.587, 1.574, 1.510 (4s, 4H), 1.364-1.225 (m, 3H), 0.562-0.482 (m, 2/3 H), -0.311 -0.391 (m, 2/3 H).
FAB-MS calc. for $C_{26}H_{30}N_4O_3S_2$ 510; found 511 (M+H, 51%).

EXAMPLE 5

N-[1(R)-[(3-hydrospiro[1H-isobenzofuran-1,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R)-[(3-hydrospiro[1H-isobenzofuran-1,4'-piperidin]-1'-yl)-carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethyl-ethyloxy)carbonyl]amino]-2-methylpropanamide

Prepared by the procedure described in Example 3, Step B. 3-Hydrospiro[1H-isobenzofuran-1,4'-piperidine] hydrochloride (10 mg, 0.044 mmol), (Bauer et al US 3985889) α(R)-[[2-[[(1,1-dimethyl-ethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid (20 mg, 0.051 mmol), HOBT (1 eq.), N-methyl-morpholine (0.01 mL, 0.093 mmol), and EDC (20 mg, 0.10 mmol). Reaction time: 5 hours. Yield: 21 mg (81%).

The product exists as a mixture of two conformers (1:1):

(^{1}H NMR $CDCl_3$): δ 8.096 (s, 1 H), 7.689 (t, 1 H), 7.341 (d, 1 H), 7.244-6.611 (m, 6 H), 5.288-5.202 (m, 1/2 H), 4.945 (br. s, 1/2 H), 4.161 (d, 1/2 H), 4.003 (d, 1/2 H), 3.338 (d, 1/2 H), 3.280-3.115 (m, 2 H), 3.005-2.861 (m, 1 H), 2.751 (d, 1/2 H), 2.416 (d, 1/2 H), 1.787-1.549 (m 3 1/2 H), 1.491, 1.461, 1.421, 1.410 (4s, 12 H), 1.281-1.212 (m, 3 H), 0.857 (t, 6 H).
FAB-MS calc. for $C_{32}H_{40}N_4O_5$ 560; found 561 (M+H, 33%).

<u>Step B:</u> <u>N-[1(R)-[(3-hydrospiro[1H-isobenzofuran-1,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride</u>

Prepared by the procedure described in Example 3, Step C. The intermediate from previous Step (20 mg, 0.04 mmol) and methanol (3 mL). Reaction time: 1 hour. Yield: 18.2 mg (93.5%).
^{1}H NMR (400 MHz, CD_3OD): The product exists as a mixture of two conformers (1:1): δ 7.621-6.568 (m, 8 H), 5.198-5.136 (m, 1 H), hidden 4.856 (br. s, 1 H), 4.098-4.045 (m, 1 H), 3.611-3.499 (m, 1 H), 3.348-3.110 (m, 5 1/2 H), 2.987-2.903 (m, 2 1/2 H), 2.618 (d, 1/2 H), 2.508 (d, 1/2 H), 1.691-1.473 (m, 8H), 1.271 (br. s, 2 1/2 H), 0.081--0.006 (m, 1/2 H).
FAB-MS calc. for $C_{27}H_{32}N_4O_3$ 460; found 461 (M+H, 96%).

<u>EXAMPLE 6</u>

<u>N-[1(R)-[(3,4-dihydro-6-methyl-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride</u>

<u>Step A:</u> <u>N-[1(R)-[(3,4-dihydro-6-methyl-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide</u>

Prepared by the procedure described in Example 3, Step B. 3,4-Dihydro-6-methylspiro[2H-1-benzopyran-2,4'-piperidine]-4-one

hydrochloride (20 mg, 0.058 mmol), (Hashigaki et al Chem. Pharm. Bull. 32 pg 3561-3568 (1984)) α(R)-[[2-[[(1,1-dimethylethoxy)-carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid) (32 mg, 0.082 mmol), HOBT (1 eq.), N-methyl morpholine (0.03 mL, 0.28 mmol), and EDC (40 mg, 0.21 mmol). Reaction time: 8 hours. Yield: 34 mg (86%).
^{1}H NMR (400 MHz, $CDCl_3$): The product exists as a mixture of two conformers (2:1): δ 8.154 (s, 2/3 H), 8.088 (s, 1/3 H), 7.626 (d, 2/3 H), 7.591-7.060 (m, 6 H), 6.725-6.688 (m, 2/3 H), 5.265- 5.168 (m, 2/3 H), 4.985-4.900 (m, 2/3 H), 4.289-4.178 (m, 2/3 H), 3.469 (s, 2/3 H), 3.229-3.064 (m, 2 2/3 H), 2.730 (t, 2/3 H), 2.562 (s, 2 1/3 H), 2.251 (d, 2 1/3 H), 2.158 (d, 2/3 H), 2.068 (d, 2/3 H), 1.680-1.541 (m, 3 H), 1.502, 1.475, 1.454, 1.427, 1.402 (5s, 15 H), 1.292-1.226 (m, 3 H), 0.616-0.532 (m, 1/3 H), -0.495 -0.590 (m, 1/3 H).
FAB-MS calc. for $C_{34}H_{42}N_4O_6$ 602; found 603. (M+H, 37%).

Step B: N-[1(R)-[(3,4-dihydro-6-methyl-4-oxospiro[2H-1-benzo-pyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

Prepared by the procedure described in Example 3, Step C. The intermediate from previous Step (20 mg, 0.029 mmol) and methanol (3 mL). Reaction time: 3 hours. Yield: 17.5 mg (96.5%).
^{1}H NMR (400 MHz, $CDCl_3$): The product exists as a mixture of two conformers (2:1): δ 7.550-6.768 (m,7 1/3 H), 5.089-5.016 (m, 2 H), hidden 4.872-4.679 (m, 1 H), 4.144-4.093 (m, 1 H), 3.569-3.485 (m, 1 H), 3.321-3.081 (m, 2 1/3 H), 2.716-2.600 (m, 1 1/3 H), 2.253, 2.236, 2.222, 2.196, 2.190, 2.155 (6s, 4 H), 1.569, 1.541, 1.475 (3s, 7 H), 1.388-1.237 (m, 3 2/3 H), 0.881-0.808 (m, 2 H), 0.434-0.420 (m, 2/3 H), 0.427-0.436 (m, 2/3 H).
FAB-MS calc. for $C_{29}H_{34}N_4O_4$ 502; found 503 (M+H, 97%).

EXAMPLE 7

N-[1(R)-[(3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl-2-amino-2-methylpropanamide hydrochloride

Step A: α(R)-[[2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-4-phenylbutanoic acid, phenylmethyl ester

A dichloromethane solution of 2(R)-amino-4-phenylbutanoic acid, phenylmethyl ester, toluenesulfonic acid salt (6.0 g, 13 mmol) was extracted with dilute sodium hydroxide solution. The organic layer was dried over $MgSO_4$ and evaporated to give a residue. To the solution of the residue, N-tert-butyloxycarbonyl-α-methylalanine (3.21g, 15.8 mmol), HOBT (1.7g, 13 mmol) in dichloromethane was added EDC (5.1 g, 26 mmol) and the mixture was stirred overnight at room temperature. The mixture was then poured into a mixture of brine and 3 N HCl and extracted with ethyl acetate. The organic extract was dried, evaporated, and purified by flash column chromatography, eluting with 40% ethyl acetate in hexane, to give the desired product (5.47g, 91%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.07 (m, 10 H), 5.15 (d, J_{AB}=12 Hz, 1 H), 5.08 (d, J_{BA}=12 Hz, 1 H), 4.86 (br. s, 1 H), 4.67-4.62 (m, 1 H), 2.61-2.53 (m, 2 H), 2.18-2.14 (m, 1 H), 2.01-1.96 (m, 1 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 9 H).

Step B: α(R)-[[2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-4-phenylbutanoic acid

The intermediate from previous Step (5.37 g, 11.8 mmol) was hydrogenated at room temperature and 1 atm of H_2 using 10% palladium on carbon as catalyst (0.5 g) for 2 hours. The catalyst was filtered through celite and evaporated to give the title compound (4.22g, 100%).

^{1}H NMR (200 MHz, CD_3OD): δ 7.804-7.143 (m, 5 H), 4.402-4.359 (m, 1 H), 2.672 (dt, 2 Hz, 6 Hz, 2 H), 2.126-2.004 (m, 2 H), 1.483, 1.444 (2s, 5 H), 1.423 (s, 9 H), 1.412 (s, 3 H).

Step C: N-[1(R)-[(3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

A solution of spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one (20 mg, 0.0.776) and the intermediate from previous Step (31 mg, 0.085 mmol) in dichloromethane was cooled to 0°C and then HOBT (1 eq.), N-methylmorpholine (0.1 mL, 0.90 mmol) and EDC (33 mg, 0.17 mmol) were added. The reaction mixture was stirred at room temperature for 3 hours, until the reaction was judged complete by TLC analysis. The solution was then washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solution was then filtered and concentrated. Purification by silica gel chromatography provided the title compound (41.6 mg, 95.5%).
^{1}H NMR (400 MHz, $CDCl_3$): The product exists as a mixture of two conformers (1:1): δ 7.853-6.925 (m, 9 H), 4.936-4.868 (m, 2 H), 4.355-4.265 (mt, 1 H), 3.605-3.565 (m, 1/2 H), 3.388-3.318 (m, 1 H), 3.022-2.965 (m, 1 H), 2.686-2.608 (m, 3 H), 2.067-1.948 (m, 2 1/2 H), 1.871-1.810 (m, 1 H), 1.580 (br. s, 2 H), 1.503, 1.488, 1.455, 1.411, 1.403 (5s, 15 H), 1.292-1.227 (m, 2 H).

Step D: N-[1(R)-[(3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl-2-amino-2-methylpropanamide hydrochloride

A solution of intermediate from previous Step (40 mg, 0.071 mmol) in ethyl acetate was cooled to 0°C. Then hydrochloric gas was bubbled into solution for 2 minutes. The reaction was stirred for 15 minutes, until TLC indicated that the reaction was complete. The solution was concentrated and the hydrochloric salt (33.8 mg, 95.5%) was used without purification.

^1H NMR(400 MHz, CD_3OD): The product exists as a mixture of two conformers (1:1): δ 8.271-8.229 (m, 1 H), 7.799 (dd, 1 3/4 Hz, 7.84 Hz, 1 H), 7.545 (q, 1 H), 7.289-7.006 (m, 7 H), 4.737-4.703 (m, 1 H), 4.277 (d, 1/2 H), 4.186 (d, 1/2 H), 3.555-3.292 (m, 1 1/2 H), 3.187-3.068 (m, 1 H), 2.809-2.724 (2m, 2 H), 2.633-2.563 (m, 1 H), 2.085-1.927 (m, 3 1/2 H), 1.645, 1.639, 1.616 (3s, 6 H), 1.677-1.603 (m, 3H) 1.316-1.279 (m, 2 H).
FAB-MS calc. for $C_{27}H_{33}N_3O_4$ 463; found 464 (M+H, 54%).

EXAMPLE 8

N-[1(R)-[(3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R-[3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methyl-propanamide.

A solution of spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one (20 mg, 0.776) and α(R)-[[2-[[(1,1-dimethylethyloxy)carbonyl]-amino]-2,2-dimethyl-1-oxoethyl]amino]-3-(phenylmethyloxy)-3-propanoic acid (32 mg, 0.085 mmol) in dichloromethane was cooled to 0°C and then HOBT (1 eq.), N-methylmorpholine (0.1 mL, 0.90 mmol) and EDC (33 mg, 0.171 mmol) were added. The reaction mixture was stirred at room temperature for 4 hours, until the reaction was judged complete by TLC analysis. The solution was then washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solution was then filtered and concentrated. Purification by silica gel chromatography provided the title compound(40.8 mg, 91%).
FAB-MS calc. for $C_{32}H_{41}N_3O_7$ 579; found 580 (M+H, 23%); [found 480 (M+H-100, 57%) loss of *t*-Boc protective group].

Step B: N-[1(R-[(3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Prepared by the procedure described in Example 3, Step D. The intermediate from previous Step (35 mg, 0.061. mmol) and ethyl acetate (10 mL). Reaction time: 1 hour. Yield: 30.2 mg (97%). ^{1}H NMR (400 MHz, CD_3OD): The product exists as a mixture of two conformers (1:1): δ 7.800-7.792- (m, 1 H), 7.533-7.578 (m, 1 H), 7.395-7.285 (m, 5 H), 7.088-7.015 (m, 2 H), 5.551-5.107 (m, 1 H), hidden 4.921-4.816 (m, 1 H), 4.535-4.518 (2s, 1 1/2 H), 4.295 (d, 1 H), 3.911-3.803 (m, 1 H), 3.717-3.703 (2s, 1 1/2 H), 3.499-3.400 (m, 1 H), 3.309-3.291 (4s, 3 1/2 H), 3.211-3.051 (m, 1 H), 2.789 (q, 1/2 H), 2.633-2.513 (AB q, 1 H), 2.060 (t, 1 H), 1.897 (d, 1/2 H), 1.821-1.725 (m, 1/2 H), 1.626-1.567 (6s, 6 H), 1.564-1.410 (m, 1/2 H), 1.301 (br. s, 1 1/2 H). FAB-MS calc. for $C_{27}H_{33}N_3O_5$ 479; found 480 (M+H, 100%).

EXAMPLE 9

N-[1(R)-[(6-chloro-3H-4-oxospiro[1H-quinazoline-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R)-[(6-chloro-3H-4-oxospiro[1H-quinazoline-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methyl-propanamide

Prepared by the procedure described in Example 3, Step B. 6-Chlorospiro(piperidine-4,2(1'H)-quinazolin)-4(3H)one hydrochloride (50 mg, 0.17 mmol), α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid (81 mg, 0.21 mmol), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (80 mg, 0.42 mmol). Reaction time: 3 hours. Yield 64.5 mg (60%). FAB-MS calc. for $C_{32}H_{39}N_6O_5Cl$ 623; found 624 (M+H, 29%).

Step B: N-[1(R)-[(6 chloro-3H-4-oxospiro[1H-quinazoline-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

Prepared by the procedure described in Example 7, Step D. Intermediate from previous Step (50 mg, 0.08 mmol). Reaction time: 1 hour. Yield: 40 mg (89.5%).
FAB-MS calc. for $C_{27}H_{31}N_6O_3Cl$ 523; found 523 (M+H, 71%).

EXAMPLE 10

N-[1(R)-[(1,4-dihydro-4-phenyl-1-oxospiro[3H-2-benzopyran-3,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)-ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: 1,4-Dihydro-4-phenylspiro(3H-2-benzopyran-3,4'-piperidine)-1-one

Prepared by the procedure described in Example 3, Step A from 1'-benzyl-1,4-dihydro-4-phenylspiro(3H-2-benzopyran-3,4'-piperidine)-1-one hydrochloride, (8 mg, 0.019 mmol) and ethanol (5 mL). Reaction time: 45 minutes. Yield 5.5 mg (98.5%).
FAB-MS calc. for $C_{19}H_{19}NO_2$ 293; found 294 (M+H, 93%).

Step B: N-[1(R)-[(1,4-dihydro-4-phenyl-1-oxospiro[3H-2-benzopyran-3,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

Prepared by the procedure described in Example 3, Step B. The intermediate from previous Step (5 mg, 0.017 mmol), α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid (12 mg, 0.030 mmol), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (12 mg, 0.060 mmol). Reaction time: 5 hours. Yield: 9.2 mg (86%).
^{1}H NMR(400 MHz, CD_3OD): The product exists as a mixture of two conformers (1:1): δ 8.185-8.072 (m, 1 1/2 H), 7.885 (s, 1/2 H), 7.710-

6.813 (m; 12 H), 5.331-5.309 (m; 1/2 H), 5.198-5.111 (m, 1/2 H), 4.710-4.605 (m, 1/2 H), 4.300-4.235 (m, 1/2 H), 3.876 (d, 1/2 H), 3.719-3.617 (m, 1 H), 3.355-3.046 (m; 1 1/2 H) 2.746 (q, 1/2 H), 2.006-1.960 (m, 1 H), 1.678-1.574 (m, 2 H), 1.438, -1.368 (m, 6 H), 1.257, 1.240, 1.227, 1.208, 1.186 (5s, 5 H).

Step C: N-[1(R)-[(1,4-dihydro-4-phenyl-1-oxospiro[3H-2-benzopyran-3,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

Prepared by the procedure described in Example 7, Step D. Intermediate from previous Step (9 mg, 0.015 mmol) and ethyl acetate (10 mL). Reaction time: 1 hour. Yield: 8 mg (97%). ^{1}H NMR(400 MHz, $CDCl_3$): The product exists as a mixture of two conformers (2:1): δ 8.347-8.333 (m, 1 H), 8.043 (t, 1/2 H), 7.662-6.869 (m, 12 1/2 H), 5.355-5.315 (m, 1/2 H), 5.108-5.061 (m, 1/2 H), hidden 4.897-4.768 (m, 1/2 H), 4.174-4.103 (m, 1/2 H), 3.717-3.526 (m, 1 H), 3.387-3.237 (m, 2 H), 3.179-3.067 (m, 1 H), 2.660 (q, 1/2 H), 2.044-1.981 (m, 1 H), 1.655-1.212 (m, 11 H), 0.964-0.820 (m, 2 1/2 H), 0.575-0.423 (m, 1/2 H), -0.271- -0.448 (m, 1/2 H).
FAB-MS calc. for $C_{34}H_{36}N_4O_4$ 564; found 565 (M+H, 25%).

EXAMPLE 11

N-[1(R)-[(3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidine]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R)-[(3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

This intermediate was prepared from α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid (903 mg, 2.3 mmol) and spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one, hydrochloride (535 mg, 2.11

mmol) (Elliott, J, et al, J. Med. Chem. 1992, 35, 3973-3976) by the procedure described in Example 25, Step A (1.25 g, 100%).
^{1}H NMR (400 MHz, $CDCl_3$): compound exists as a mixture of conformers (ratio 2:1): δ 8.42, 8.31 (2s, 1 H), 7.79, 7.75 (2 dd, 1.6 Hz, 7.8 Hz, 1 H), 7.66, 7.56 (2d, 8.0 Hz, 7.6 Hz, 1 H), 7.47-6.78 (m, 8 H), 5.37-5.15 (m, 1 H), 4.98, 4.94 (2 br. s, 1 H), 4.24, 4.18 (2 br. d, 1 H), 3.40, 3.32 (2 br. d, 2 H), 3.23-3.02 (m, 3 H), 2.73 (dt, 3 Hz, 13 Hz, 1 H), 2.47 (d, 2 Hz, 1/3 H), 2.17 (d, 16.6 Hz, 2/3 H), 2.08 (d, 16.7 Hz, 2/3 H), 1.84 (br. s, 2 H), 1.70-1.60 (br. dd, 1 H), 1.3-1.2 (br. dd, 1 H), 0.56 (dt, 4.6, 13.8 Hz, 2/3 H), -0.55 (dt, 4.6, 13.8 Hz, 2/3 H). FAB-MS: calc. for $C_{33}H_{40}N_4O_6$, 588; found 595 (M+Li, 100%).

Step B: N-[1(R)-[(3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a stirred solution of the intermediate prepared in Step A (1.0 g, 1.7 mmol) in methanol (5 mL) was added concentrated hydrochloric acid (5 mL). The reaction mixture was stirred at room temperature for one hour and 20 mL of toluene was added and the mixture was evaporated in vacuo. This procedure was repeated twice to give the title compound (0.87 g, 98%).
^{1}H NMR (400 MHz, CD_3OD): compound exists as a mixture of conformers (ratio 2:1): δ 7.76-6.90 (m, 10 H), 5.11 (dd, 5,11 Hz, 1 H), 4.16, 4.11 (2 td, 2.0 Hz, 14 Hz, 1 H), 3.60, 3.33 (2 md, 14 Hz, 1 H), 3.25-3.10 (m, 2 H), 2.92-2.67 (m 2 H), 2.30-2.17 (AB, centered at w.23, 16.7 Hz, 2 H), 2.85-2.80 (br. d, 1/3 H), 1.60, 1.59 (2s, 6 H), 1.70-1.50 (m, hidden), 1.40-1.30 (md, 1 H), 0.47 (dt, 5.5, 13.5 Hz, 2/3 H), -0.38 (dt, 5.5, 13.5 Hz, 2/3 Hz). FAB-MS: calc. for $C_{28}H_{32}N_4O_4$, 488; found 489 (M+H, 100%).

EXAMPLE 11A

N-[1(R)-[(3,4-dihydro-4(RS)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide

To a stirred solution of the title compound in Example 11 (55 mg, 0.09 mmol) in methanol (5 mL) at 0°C, was added sodium borohydride (16 mg, 0.4 mmol) in several portions. After stirred at 0°C for 30 minutes the mixture was evaporated to dryness and dissolved in dichloromethane and purified by flash column eluting with 10% methanol in dichloromethane to give the title compound (35 mg, 78%). ^{1}H NMR (400 MHz, CD_3OD): compound exists as a mixture of 2 diastereomers (1:1) and each isomer exists as two conformers (ratio 2:1): δ 7.89-6.66 (m, 9 H), 5.14-5.06 (m, 1 H), 4.52-4.45 (2 dd, 1 H), 4.22-4.10 (2 md, 1 H), 3.58-3.44 (2 md, 1 H), 3.25-3.14 (m, 2 H), 3.10-2.59 (4 dt, 1 H), 2.02 (dd, 6.2, 14.7 Hz, 1/3 H), 1.79-1.74 (dd, 1/3 H), 1.60-1.40 (m, 3 H), 1.37, 1.31,1.28, 1.28, 1.26 (4 s, 6 H), 1.3-1.05 (m, hidden), 0.71, 0.49 (2 dt, 5.6,13.5 Hz, 2/3 H), -0.20, -0.47 (2 dt, 4.6, 13.5 Hz, 2/3 H). FAB-MS: calc. for $C_{28}H_{34}N_4O_4$, 490; found 491 (M+H, 100%).

EXAMPLE 12

N-[1(R)-[(3,4-dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: 3,4-Dihydrospiro[2H-1-benzopyran-2,4'-piperidine]

To a stirred solution of the spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one, hydrochloride (53 mg, 0.21 mmol) in methanol (5 mL) at 0°C, was added sodium borohydride (38 mg, 1 mmol) in several portions. After 30 minutes the mixture was evaporated and then treated with concentrated hydrochloric acid (2 mL) for 30 min. Evaporation gave a residue which was hydrogenated with palladium on carbon (10%, 10 mg), H_2 (1 atm) in ethanol for two hours. Filtration to remove the catalyst gave the crude intermediate (89 mg) which was used without further purification.
^{1}H NMR (400 MHz, CD_3OD): 7.07 (appears as d, 5 Hz, 2 H), 6.84 (appears as t, 7 Hz, 2 H), 7.07-7.08 (m, 4 H), 2.82 (t, 7 Hz, 2 H), 2.02

(br. d, 14.5 Hz, 2 H), 1.90-1.85 (m, 4 H). EI-MS: calc. for $C_{13}H_{17}NO$, 203; found 203 (M^+, 45%)

Step B: N-[1(R)-[(3,4-dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

This intermediate was prepared from the product of Step A and α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid following standard peptide coupling methods.

^{1}H NMR (400 MHz, $CDCl_3$): compound exists as a mixture of conformers (ratio 2:1): δ 8.04, 8.02 (2s, 1 H), 7.70, 7.61 (2d, 8 Hz, 1 H), 7.49-6.66 (m, 1 H), 4.92 (br. s, 1 H), 4.30-4.20 (m, 1 H), 3.4-3.1 (m, 4 H), 2.85-2.45 (m, 3 H), 1.68 (t, 7.6 Hz, 1 H), 1.49, 1.45, 1.44, 1.43, 1.41 (5 s, 12 H), 1.30-1.21 (m, 3 H), 1.11-1.07 (dd, 2.5, 14 Hz, 1/3 H), 0.68 (dt, 4.5 Hz, 13 Hz, 1/3 H), -0.33--0.43 (dt, 1/3 H). FAB-MS: calc. for $C_{33}H_{42}N_4O_5$, 574; found 575 (M+H, 35%).

Step C: N-[1(R)-[(3,4-dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

The title compound was prepared from the intermediate in Step B according to the procedure described in Example 11, Step B. (90%).

^{1}H NMR (400 MHz, CD_3OD): compound exists as a mixture of conformers (ratio 2:1): δ 8.31,8.21 (2 d, 6.6 Hz, 2/3 H), 7.58, 7.52 (2 d, 7.8 Hz, 1 H), 7.37 (d, 8.2 Hz, 1 H), 7.15-6.60 (m, 6 1/3 H), 5.17-5.13 (m, 1 H), 4.14 (br. d, 13.2 Hz, 1 H), 3.35-3.10 (m 3 H), 2.90-2.45 (m, 3 H), 1.70 (t, 6.9 Hz, 1 H), 1.60 (s, 6 H), 1.60-1.40 (m, hidden), 1.40-1.20 (m, 2 H), 1.11 (br. d, 12.7 Hz, 2/3 H), 0.57 (dt, 4.3, 13 Hz, 2/3 H), -0.31 (dt, 4.3, 13, 2/3 H). FAB-MS: calc. for $C_{28}H_{34}N_4O_3$, 474; found 475 (M+H, 60%).

EXAMPLE 13

N-[1(R)-[(3,4-dihydro-6-methanesulfonylamino-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

The title compound was prepared from α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid and 3,4-dihydro-6-methanesulfonylamino-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidine] following procedures described in Example 10, Steps A and B.

N-[1(R)-[(3,4-dihydro-6-methanesulfonylamino-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide.

^{1}H NMR (400 MHz, $CDCl_3$): compound exists as a mixture of conformers (ratio 2:1): δ 8.60, 8.36 (2 br. s, 1 H), 7.63-6.81 (m, 8 H), 5.20 (br. s, 1 H), 5.10-5.02 (br. m, 1 H), 3.45-3.30 (br. m, 1 H), 3.25-3.10 (br. m, 2 H), 2.97, 2.95 (2s, 3 H), 2.75-2.56 (m, 1 H), 2.28 (v. br. s, 1 H), 2.18 (d, 16.6 Hz, 1 H), 2.05 (d, 16.6 Hz, 1 H), 1.86-1.45 (m, hidden), 1.51, 1.46, 1.44, 1.43, 1.42, 1.39 (6 s, 12 H), 1.30-1.20 (m, 2 H), 0.55-0.45 (m, 2/3 H), -0.55--0.65 (m, 2/3 H). FAB-MS: calc. for $C_{34}H_{43}N_5O_8S$, 681; found 688 (M+Li, 40%).

N-[1(R)-[(3,4-dihydro-6-methanesulfonylamino-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride.

^{1}H NMR (400 MHz, CD_3OD): compound exists as a mixture of conformers (ratio 2:1): δ 7.63-6.92 (m, 8 H), 5.14-5.08 (m, 1 H), 4.18-4.08 (2 md, 1 H), 3.62-3.51 (2 md, 1 H), 3.25-3.10 (m, 2 H), 2.91, 2.89 (2 s, 3 H), 2.78-2.67 (2 dd, 2 Hz, 15 Hz, 2 H), 2.27 (d, 16.7 Hz, 1 H), 2.19 (d, 16.6 Hz, 1 H), 1.86-1.80 (m, 1/3 H), 1.80-1.50 (m, hidden), 1.60, 1.59, 1.48 (3s, 6 H), 1.40-1.30 (m, 1 H), 0.47 (dt, 4.8 Hz, 13 Hz,

2/3 H), -0.39 (dt, 4.8 Hz, 13 Hz, 2/3 H). FAB-MS: calc. for $C_{29}H_{35}N_5O_6S$, 581; found 582 (M+H, 75%).

EXAMPLE 14

N-[1(R)-[(3,4-dihydro-4(RS)-hydroxy-6-methanesulfonylamino-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide

The title compound was prepared from the title compound in Example 13 following the procedure described in Example 11A. ^1H NMR (400 MHz, CD_3OD): compound exists as a mixture of 2 diastereomers (1:1) and each isomer exists as two conformers: δ 7.62-7.50 (m, 1 H), 7.42-7.29 (m, 2 H), 7.17-6.98 (m, 4 H), 6.68 (d, 8.7 Hz, 1 H), 5.15-5.05 (m, 1 H), 4.75-4.65 (m, 1/3 H), 4.57 (dd, 7 Hz, 9 Hz, 1/3 H), 4.44 (dd, 6.5 Hz, 9.0 Hz, 1/3 H), 4.21-4.07 (m, 1 H), 3.56-3.44 (m, 1 H), 3.28-3.12 (m, 3 H), 3.08-3.01 (m, 2/3 H), 2.89, 2.86 (2s, 3 H), 12.82-2.55 (m, 1 H), 2.03 (dd, 6.0 Hz, 13.8 Hz, 1/2 H), 1.86 (dd, 6.0, 13.7, 1/2 H), 1.70-1.35 (m, 3 H), 1.33, 1.32, 1.31, 1.28, 1.24 (5s, 6 H), 1.33-1.29 (m, hidden), 1.06 (br. d, 13 Hz, 1/3 H), 0.71 (dt, 4.6 Hz, 13 Hz, 1/3 H), 0.49 (dt, 4.6 Hz, 13 Hz, 1/3 H), -0.21 (dt, 4.6 Hz, 13 Hz, 1/3 H), -0.49 (dt, 4.6 Hz, 13 Hz, 1/3 H). FAB-MS: calc. for $C_{29}H_{37}N_5O_6S$, 583; found 584 (M+H, 20%).

EXAMPLE 15

N-[1(R)-[(2-acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide, hydrochloride

Step A: 1,3-dihydro-1,3-dihydroxyspiro[4H-2-benzofuran-4,4'-piperidine]-1'-carboxylic acid, 1,1-dimethylethyl ester

To a stirred solution of spiro[1H-indene-1,4'-piperidine]-1'-carboxylic acid, 1,1-dimethylethyl ester (800 mg, 2.8 mmol) in methanol (50 mL) at -78°C, was bubbled ozone until the solution turned

blue. The mixture was let stand at that temperature for 20 minutes, then purged with nitrogen. Dimethyl sulfide (3 mL) was added and the mixture was warmed to room temperature and stirred for two hours. Evaporation of the solvent gave a crude product (940 mg) which was used without purification.

Step B: 1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidine]-1'-carboxylic acid, 1,1-dimethylethyl ester

The intermediate of Step A (100 mg) was stirred in methanol (2 mL) saturated with ammonia for one day, and evaporated to remove ammonia. The residue was redissolved in methanol (3 mL) and sodium cyanoborohydride (50 mg, excess) was added. The mixture was stirred overnight. Evaporation and purification gave the amine. ^1H NMR (400 MHz, CD_3OD): δ 7.35-6.96 (m, 4 H), 4.00 (s, 2 H), 3.14 (s, 2 H), 3.90 (br. s, 2 H), 2.05 (br. s, 2 H), 1.95 (br. t, 2 H), 0.69 (d, 2 H), 1.49 (s, 9 H).

Step C: 2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidine]-1'-carboxylic acid, 1,1-dimethylethyl ester

The intermediate (16 mg) from Step A was treated with pyridine (2 mL) and acetic anhydride (2 mL) for 2 hours and the reaction mixture was evaporated in vacuo to afford the desired compound (12 mg).

^1H NMR (400 MHz, $CDCl_3$, compound exists as a mixture of 3:1 rotamers): δ 7.36-7.05 (m, 4 H), 4.72 (s, 2/4 H), 4.65 (s, 6/4 H), 4.10-4.00 (br. d, 12.8 Hz, 2 H), 3.85 (br. s, 3/4 H), 3.65 (s, 1/4 H), 3.11 (t, 13.1 Hz, 3/4 H), 3.00 (t, 13.1 Hz, 1/4 H), 2.19 (s, 3/4 H), 2.18 (s, 9/4 H) 2.00-1.80 (m, 2 H), 1/65-1.47 (m, 2H, hidden), 1.47 (s, 9/4 H), 1.45 (s, 27/4 H).

Step D: 2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidine]

To a solution of intermediate from Step C (12 mg) in ethyl acetate (5 mL) at 0°C, was bubbled HCl (gas) until it is saturated. After

30 minutes, the reaction mixture was evaporated in vacuo to afford the desired intermediate.
^{1}H NMR (400 MHz, CD_3OD): δ 7.47-7.19 (m, 4 H), 4.79 (s, 2 H), 3.96 (s, 2 H), 3.36 (br. d, 6.7 Hz, 2 H), 2.30-2.24 (m, 1 H), 2.21 (s, 3 H), 1.76 (d, 13 Hz). FAB-MS: calc. for $C_{15}H_{20}N_2O$, 244; found 245 (M+1, 100%)

Step E: N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methyl-propanamide

Title compound was prepared from the intermediate from Step D according to the procedures described previously.

EXAMPLE 16

N-[1(R)-[1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: methyl α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-3[(2',6'-difluorophenyl)-methoxy]propanic acid

Oil free sodium hydride (prepared from 60% oil dispersion of sodium hydride by washing with hexanes (3X), 1.2 g, 30.0 mmole), suspension in 30 mL N,N-dimethylformamide was added N-t-butyloxycarbonyl-(D)-serine (3.07 g, 15.0 mmole) in 10 mL N,N-dimethylformamide at room temperature. When no more gas evolves 2,6-diflorobenzyl bromide (2.68 g, 12.9 mmole) was added. After 18 hours stirring at room temperature, iodomethane (1.0 mL, 16.0 mmole) was added to the reaction mixture. The mixture was stirred another 1 hour, and then poured into water, and extracted with ethyl ether. The organic layer was washed sequentially with water (5X), brine and dried over sodium sulfate, filtered and concentrated. The residue was dissolved in 20 ml of chloroform and BOC-α-methylalanine, EDC,

HOBT, and Et3N were added at room temperature. After 3 hours the reaction mixture was poured into water and extracted with methylene chloride. The organic layer was dried over sodium sulfate and concentrated. The title compound was obtained after purification by chromatography, (hexane/ethyl acetate:3/1) to give 2.37 g (35%). ^{1}H NMR (300 MHz, $CDCl_3$ mixture of rotamers): 7.27 (m, 1 H), 7.02-6.88 (m, 2 H), 4.95 (m, 1 H), 4.72 (dt, 8, 3 Hz, 1 H), 4.58 (br. s, 2 H), 3.90 (m, 1 H), 3.78 (s, 1 H), 3.69 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 3 H), 1.41 (s, 9 H).

Step B: N-[1(R)-[1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

A solution of the intermediate obtained from this Example, Step A (2.37 g, 5.29 mmole) in 30 mL of methanol was added lithium hydroxide (340 mg, 8.1 mmole) in 3 mL of water. After 2 hours stirring at room temperature, the reaction mixture was concentrated, and then diluted with water, extracted with ethyl ether. The organic layer was discarded. The aqueous layer was acidified with 1 N hydrochloric acid to pH=1.5 and extracted with ethyl ether (3X). The organic layer was dried over sodium sulfate, filtered, and concentrated to give 2.18 g (95%) of acid. The title compound was prepared from acid (78 mg, 0.18 mmole), and 1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidine hydrochloride (50 mg, 0.165 mmole) by the procedure described in Example 20, Step B (use hydrochloride in ethyl ether instead of trifluoroacetic acid) to give 48 mg (44%). ^{1}H NMR (400 MHz, CD_3OD mixture of rotamers): 7.39 (m, 2 H), 7.22 (m, 1 1/2 H), 7.03 (m, 3 1/2 H), 5.14 (dd, 13, 7 Hz, 1 H), 4.66 (d, 16 Hz, 2 H), 4.49 (m, 1 H), 4.09 (m, 1 H), 3.92 (br. s, 2 H), 3.76 (m, 2 H), 3.25 (m, 1 H), 2.97 (s, 3/2 H), 2.96 (s, 3/2 H), 2.87 (m, 1 H), 1.95 (m, 1 H), 1.76 (m, 3 H), 1.61 (s, 3/2 H), 1.57 (s, 3 3/2 H), FAB-MS: 565 (M+1).

EXAMPLE 17

N-[1(R)-[(1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methylpropanamide hydrochloride

Step A: t-butyloxycarbonyl-(D)-hexahydrohomophenylalanine

A solution of t-butyloxycarbonyl-(D)-homophenylalanine (100 mg, 0.358 mmole) in 1 mL acetic acid was hydrogenated over PtO_2 at one atmosphere for 16 hours. The mixture was filtered through Celite and the filtrate concentrated and azeotroped with toluene. ^{1}H NMR (400 MHz, $CDCl_3$): 5.03 (d, 8 Hz, 1 H), 4.22 (m, 1 H), 1.82 (m, 1 H), 1.64 (m, 6 H), 1.41 (s, 9 H), 1.20 (m, 6 H), 0.84 (m, 2 H).

Step B: benzyl α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-4-cyclohexylbutanoic acid

A solution of BOC-D-homaphenylalanine in acetic acid was hygrogenated over PtO_2 at one atmosphere for 16 hours. The mixture was filtered through celite and concentrated. To this residue (44 mg) in 15 mol DMF was added benzyl bromide (198 ml) and K_2CO_3 (970 mg) at room temperature. After stirring overnight, the mixture was poured into 200 ml of ether and washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 7.5% ethyl acetate in hexanes) to provide 534 mg (95%) of this intermediate. A solution of 534 mg of this material in 10 ml 1:1 TFA/CH_2Cl_2 was stirred for 1 hour then stripped and azeotroped from toluene. The residue was dissolved in 10 ml CH_2Cl_2 and cooled to 0°C. BOC-α-methylalanine (362 mg), EDC, HOBT and NMM were added and stirred overnight. The solution was poured into 250 ml ethyl acetate and washed sequentially with 1N $NaHSO_4$ (aq.), water and saturated aqueous $NaHCO_3$. The organic phase was dried, filtered and concentrated. Purified by flash chromatography (silica gel, ethyl acetate/hexanes) to provide 638 mg of the title compound.

^1H NMR (200 MHz, $CDCl_3$): .8-.95 (m, 3 H), 1.05-1.3 (m, 7 H), 1.4-1.9 (m, 19 H), 2.15 (m, 2 H), 4.59 (m, 1 H), 4.87 (m, 1 H), 5.18 (m, 2 H), 6.96 (m, 1 H), 7.35 (m, 5 H). FAB-MS calculated for $C_{26}H_{40}N_2O_5$ 460; found 461.5 (M+H).

Step C: N-[1(R)-[(1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methylpropanamide hydrochloride

A mixture of 638 mg of the intermediate obtained in Step B and 100 mg of 10% Pd on carbon was stirred under a balloon containing H_2 for 4 hours. The mixture was filtered through Celite and the filtrate was concentrated. A portion (87 mg) of this residue was dissolved in 2 ml CH_2Cl_2 and 49.8 mg of 1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidine hydrochloride, EDC and HOBT were added and stirred for 16 hours. The solution was poured into 200 ml ethyl acetate and washed sequentially with 1N $NaHSO_4$ (aq.), water and saturated aqueous $NaHCO_3$. The organic phase was dried, filtered and concentrated. Purified by flash chromatography (silica gel, 60% ethyl acetate/hexanes) to provide 55 mg (47%) of this intermediate. All of this material was dissolved in 2 ml 1:1 TFA/CH_2Cl_2 and stirred for 1/2 hour. The solution was stripped and the residue was purified by flash chromatography (silica gel, methanol, NH_4OH(aq.), CH_2Cl_2). The compound was then dissolved in CH_2Cl_2, treated with HCl in ether and concentrated to provide the title compound.
^1H NMR (400 MHz, CD_3OD): .93 (m, 2 H), 1.15-1.3 (m, 6 H), 1.55-1.8 (m, 1 H), 2.06 (dt, 15, 4 Hz, 1 H), 2.88 (m, 1 H), 2.97 (m, 1 H), 3.35 (m, 2 H), 3.8-4.1 (m, 3 H), 4.51 (m, 1H), 4.83 (m, 1H), 7.06 (q, 7 Hz, 1H), 7.22 (m, 2H), 7.37 (d, 8 Hz, 1H).
FAB-MS calculated for $C_{27}H_{42}N_4O_4S$ 518; found 519.7 (M+H)

EXAMPLE 18 (METHOD 1)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: 1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine]hydrochloride

To a solution of 1.20 g (5.8mmol) of 1'-methyl-1,2-dihydro-spiro[3H-indole-3,4'-piperdine] (prepared as described in H. Ong et al *J. Med. Chem.* **1983**, *23*, 981-986) in 20 mL of dry dichloromethane at 0°C was added triethylamine (0.90 mL; 6.4 mmol) and methanesulfonyl chloride (0.49 mL; 6.35 mmol) and stirred for 30 min. The reaction mixture was poured into 15 mL of saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (2X10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous potassium carbonate, filtered and the solvent removed under reduced pressure to yield 1.44 g of the methanesulfonamide derivative as pale yellow oil which was used without purification.

To a solution of above crude product in 20 mL of dry 1,2-dichloroethane at 0°C was added 1.0 mL (9.30 mmol) of 1-chloroethyl chloroformate, and then stirred at RT for 30 min and finally at reflux for 1h. The reaction mixture was concentrated to approximately one third of the volume and then diluted with 20 mL of dry methanol and refluxed for 1.5h. The reaction was cooled to RT and concentrated to approximately one half of the volume. The precipitate was filtered and washed with a small volume of cold methanol. This yielded 1.0 g of the piperidine HCl salt as a white solid. The filtrate was concentrated and a small volume of methanol was added followed by ether. The precipitated material was once again filtered, washed with cold methanol, and dried. This gave an additional 0.49 g of the desired product. Total yield 1.49 g (70%).

^{1}H NMR($CDCl_3$, 200MHz) δ 7.43-7.20 (m, 3H), 7.10 (dd, 1H), 3.98 (bs, 2H), 3.55-3.40 (bd, 2H), 3.35-3.10 (m, 2H), 2.99 (s, 3H), 2.15 (t, 2H), 2.00 (t, 2H).

Step B: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethylethoxy)carbonyl]amino-2-methyl-propanamide

To 0.35g (1.15 mmol) of (2R)-2-[(1,1-dimethylethoxy)-carbonyl]amino-3-[2-(phenylmethyloxy)ethyl]-1-propanoic acid in 13 mL of dichloromethane was added 1,2-dihydro-1-methanesulfonylspiro-[3H-indole-3,4'-piperdine] hydrochloride (0.325 g; 1.07 mmol), 0.18 mL (1.63 mmol) of N-methylmorpholine, 0.159 g (1.18 mmol) of 1-hydroxybenztriazole(HOBT) and stirred for 15 min. EDC (0.31 g; 1.62 mol) was added and stirring was continued for 1h. An additional 60 μL of N-methylmorpholine was added and stirred for 45 min. The reaction mixture was poured into 5 mL of water and the organic layer was separated. The organic layer was washed with 5 mL of 0.5N aqueous hydrochloric acid and 5 mL of saturated aqueous sodium bicarbonate solution. The combined organics were dried over anhydrous magnesium sulfate, and concentrated to yield 0.627 g of the product as a yellow foam which was used without purification.

To a 0.627 g (1.07 mmol) of the above product in 5 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and stirred at RT for 75 min. An additional 1.00 mL of trifluoroacetic acid was added and stirred for 10 min. The reaction mixture was concentrated, diluted with 5.0 mL of dichloromethane and carefully basified by pouring into 10 mL of 10% aqueous sodium carbonate solution. The organic layer was separated and the aqueous layer was further extracted with 2X15 mL of dichloromethane. The combined organics were washed with 5 mL of water, dried over potassium carbonate, filtered and concentrated to give the 0.486 g of the amine as a light yellow foam which was used without purification.

To 0.486 g (1.01 mmol) of the amine and 10 mL of dichloromethane was added 0.26g (1.28 mmol) of 2-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methyl-propanoic acid, 0.173 g (1.28 mmol) of 1-hydroxybenztriazole (HOBT) and EDC (0.245 g; 1.28 mol) and stirried at RT overnight. The reaction mixture was poured into 5.0 mL

of water and the organic layer was separated. The aqueous layer was back extracted with 5 mL of dichloromethane. The combined organics were washed with 5.0 mL of 0.5N aqueous hydrochloric acid, 5 mL of saturated aqueous sodium bicarbonate solution dried over anhydrous magnesium sulfate, and concentrated to yield 0.751 g of the crude product as a yellow foam. A solution of this crude product in dichloromethane was chromatographed on 25 g of silica gel and eluted first with hexanes/acetone/dichloromethane (70/25/5) and then with hexanes/acetone/dichloromethane (65/30/5). This gave 0.63 g of the title compound as a white solid.

^{1}H NMR($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86 (s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To 0.637 g (0.101 mmol) of the intermediate from Step B in 5 mL of dichloromethane was added 2.5 mL of trifluoroacetic acid and stirred at RT for 30 min. The reaction mixture was concentrated to an oil, taken up in 10 mL of ethyl acetate and washed with 8 mL of 10% aqueous sodium carbonate solution. The aqueous layer was further extracted with 5 mL of ethyl acetate. The combined organics were washed with 10 mL of water, dried over magnesium sulfate, filtered and concentrated to give the 0.512 g of the free base as a white foam.

To 0.512 g of the free base in 5 mL of ethyl acetate at 0°C was added 0.2 mL of saturated hydrochloric acid in ethyl acetate and stirred for 1.5 h. The white precipitate was filtered under nitrogen, washed with ether, and dried to give 0.50 g of the title compound as a white solid

^{1}H NMR (400MHz, CD_3OD) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 19 (METHOD 2)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino-2-(phenylmethoxy)ethyl]-1-propanoic acid allyl ester

Prepared from (2R)-2-[(1,1-dimethylethoxy)carbonyl]-amino-3-(phenylmethyloxy)ethyl-propanoic acid and allyl alcohol by carrying out the coupling reaction in CH_2Cl_2 in the presence of EDC and DMAP.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.25 (s, 5H), 5.8 (m, 1H), 5.2 (dd, 2H), 5.0 (bs, 1H), 4.7 (m, 1H), 4.6 (m, 2H), 4.4 (dd, 2H), 3.9 (dd, 1H), 3.6 (dd, 1H), 1.45 (d, 6H), 1.39 (s, 9H).

Step B: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino-2-(phenylmethyloxy)ethyl)-1-propanoic acid

To a stirred solution of the crude intermediate obtained in Step A (6.7 g, 15.9 mmol), tetrakis (triphenylphosphine)-palladium (1.8 g, 0.1 eq) and, triphenyl phosphine (1.25 g, 0.3 eq) was added a solution of potassium-2-ethyl hexanoate (35 mL, 0.5M solution in EtOAc). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 1h and then diluted with ether (100 mL) and poured into ice-water. The organic layer was seperated and the aqueous fraction was acidified with citric acid (20%), then extracted with EtOAc. The EtOAc extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated to give the title compound as a solid.

^{1}H NMR (400Hz, CD_3OD) δ 7.3 (s, 5H), 4.7 (m, 1H), 4.5 (s, 2H), 4.0 (m, 1H), 3.6 (m, 1H), 1.4 (d, 6H), 1.3 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methyl-propanamide

To a solution of 1.0 g (3.44 mmol) of 1-methanesulfonyl-spiro[indoline-3,4'-piperidine] hydrochloride, 1.44 g (3.78 mmol) of (2R)-[[-2-(1,1-dimethylethoxy)carbonyl)amino]-2,2-dimethyl-1-oxoethyl]-amino-2-(phenylmethyloxy)ethyl)-1-propanoic acid, N-methyl morpholine (0.58 mL; 5.20 mmol), and 1-hydroxybenztriazole (HOBT) (0.58 g; 3.78 mmol), in 50 mL of dichloromethane was added EDC (1.03 g; 5.20 mmol) and stirred at RT for 16h. The reaction mixture was diluted with an additional 50 mL of dichloromethane and washed with aqueous sodium bicarbonate solution (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Flash chromatography (50 g silica gel) of the crude oily residue gave 2.148 g (90%) of the desired material as a colorless foam.

^{1}H NMR ($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86 (s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step D: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of 2.148 g (3.41 mmol) of the intermediate from Step C in 10 mL of dichloromethane was added 5 mL of trifluoroacetic acid and stirred for 1h. The reaction mixture was concentrated and basified with 100 mL of 5% aqueous sodium carbonate solution and extracted with dichloromethane (3X50 mL). The combined organics were washed with brine (50 mL), dried over anhydrous potassium carbonate, filtered, and concentrated to yield a

colorless foam. To a solution of the foam in 25 mL of ethyl acetate at 0°C was added 4 mL of 1M solution of hydrochloric acid in ethyl acetate. The precipitate was filtered and washed first with ethyl acetate and then with ethyl acetate-ether (1:1), dried to yield 1.79 g (93%) of the title compound as a colorless solid.

^{1}H NMR(400MHz, CD_3OD) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 20

N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-bromo-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-bromo-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)-ethyl]-2-[(1,1-dimethylethoxy)-carbonyl]amino-2-methylpropanamide

To a solution 300 mg (1.03 mmol) of 1-methanesulfonyl-spiro-[3H-indole-3,4'-piperidine] hydrochloride in 5 mL of glacial acetic acid was added 0.28 g (2.06 mmol) of bromine and stirred at RT for 1h. The reaction mixture was concentrated to dryness, basified with 10 mL of 5% aqueous sodium carbonate solution, and extracted with dichloromethane (3X10 mL). The combined organics were washed with brine (10 mL), dried over anhydrous potassium carbonate, filtered, and concentrated to yield 0.25 g of a crude product as a yellow oil which was used without purification.

Step B:

To a solution of the above crude product in 10 mL of dichloromethane was added 0.43 g (1.13 mmol) of the intermediate

from Example 19 Step B, 0.17 g (1.13 mmol) of HOBT, and 0.34 g (1.70 mmol) of EDC and stirred at RT for 16h. The reaction mixture was diluted with 15 mL of ether and washed with 10% aqueous citric acid (15 mL), saturated sodium bicarbonate solution (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give a crude oily product. This residue was purified was flash chromatography (15 g SiO_2; CH_2Cl_2-Acetone(10:1) as eluent) to yield 0.184 g (26% for 2 steps) of the coupled material as colorless foam.

To 0.184 g (0.26 mmol) of the above material in 2 mL of dichloromethane was added 2 mL of trifluoroacetic acid and stirred at RT for 1h. The reaction mixture was evaporated to dryness to yield 0.146 g (93%) of the title compound as a white solid.
FAB-MS: calculated for $C_{27}H_{34}BrN_4O_5S$ 608; found 609.5

EXAMPLE 21

N-[1(R)-[(1,2-Dihydro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide dihydrochloride

Step A: Spiro[3H-indole-3,4'-piperidine]

To a solution of 1.0 g (5.0 mmol) of 1'-methyl-spiro[3H-indole-3,4'-piperidine] (prepared as described in H. Ong et al *J. Med. Chem.* **1983**, *23*, 981-986) and 1.0 g of powdered potassium carbonate in 30 mL of dry dichloromethane at RT was added to 0.50 g of cyanogen bromide and stirred for 1h. The reaction mixture was filtered through a pad of celite and washed with chloroform-methanol (95:5). The filtrate was concentrated and the residue was flushed through a pad of silica gel with chloroform-methanol (95:5) as eluent. This gave ~1.2 g of a yellow oil which was used without purification.

To a suspension of above compound in 30 mL of dry DME at 0°C was added 0.30 g of lithium aluminum hydride and warmed to RT and finally refluxed for 1h. The reaction mixture was cooled to 0°C and quenched with 0.30 mL of water, 0.30 mL of 15% aqueous of sodium hydroxide solution, and 0.90 mL of water. The solids were filtered off through a pad of celite and washed well with chloroform-

methanol (10:1). Concentration of the filtrate gave 0.74 g of the compound as a yellow foam. This material was a 1:1 mixture of the title compound and 1'-methyl-spiro[3H-indole-3,4'-piperidine] .

Step B: (2R)-[[-2-[[1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid benzyl ester

To 5.0 g (16.5 mmol) of the commercially available N-t-BOC-D-tryptophan in 100 mL of chloroform was added 1.80 mL (16.5 mmol) of benzyl alcohol, 0.20 g (1.65 mmol) of 4-N,N-dimethylamino pyridine (DMAP), and 3.20 g of EDC and stirred for 16h. The reaction mixture was poured into 100 mL of water and the organic layer was seperated. The aqueous was further extracted with 2X100 mL of chloroform. The combined organics were washed with 50 mL of 10% aqueous citric acid, 100 mL of 10% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil.

To a solution of this oil in 10 mL of dichloromethane was added 20 mL of trifluoroacetic acid and stirred for 1h. The reaction mixture was concentrated, basified carefully with saturated aqueous sodium bicarbonate solution, and extracted with chloroform (2X100 mL). The combined organics were washed with brine (100 mL), dried over potassium carbonate, filtered, and concentrated to give 5.46 g of the amine as a brown oil which was used without purification.

To 5.46 g of the above product in 100 mL of chloroform was added 3.40 g (22.2 mmol) of HOBT, 4.60 g (22.2 mmol) of N-BOC-α-methyl alanine, and 5.32 g (28.0 mmol) of EDC and stirred for 16h. The reaction mixture was poured into 100 mL of water and the organic layer was seperated. The aqueous was further extracted with 2X100 mL of chloroform. The combined organics were washed with 50 mL of 10% aqueous citric acid, 100 mL of 10% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give 6.94 g of the product as a thick oil. Flash

chromatography (200 g SiO_2; hexane-ethyl acetate as eluent) gave 4.75 g of the desired material as a colorless foam.
^{1}H NMR ($CDCl_3$, 200MHz) δ 8.48 (bs, 1H), 7.54 (bd, 1H), 7.38-7.23 (m, 3H), 7.19 (bd, 2H), 7.15-7.00 (m, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 5.06 (bs, 2H), 4.95 (ddd, 1H), 3.30 (2dd, 2H), 1.40 (s, 15H)

Step C: (2R)-[[-2-[[1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid

To a solution of 4.75 g of the material from Step B in 100 mL of ethanol was added 1.0 g of 10% Pd/C and stirred at RT under a H_2 balloon for 18h. The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give 2.96 g of the acid as a colorless foam.
^{1}H NMR ($CDCl_3$, 200MHz) δ 8.60 (bs, 1H), 7.55 (d, 1H), 7.26-6.90 (m, 3H), 6.88 (bd, 1H), 4.80 (m, 1H), 3.32 (2dd, 2H), 1.37 (s, 3H), 1.35 (s, 12H)

Step D: N-[1(R)-[(1,2-Dihydro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[(1,1-dimethylethoxy)-carbonyl]amino-2-methylpropanamide

To a solution of 0.122 g (0.542 mmol) of a 1:1 mixture of the intermediate from step A and 1'-methyl-spiro[3H-indole-3,4'-piperidine] in 5 mL of dry chloroform at RT was added 0.105 g (0.271 mmol) of the intermediate from Step C, 41 mg (0.271 mmol) of HOBT, and 80 mg (0.41 mmol) of EDC and stirred at RT for 2h. The reaction mixture was diluted with 10 mL of chloroform was washed with saturated aqueous sodium bicarbonate solution (10 mL) and 10 mL of brine, dried over anhydrous potassium carbonate, filtered and concentrated. Flash chromatography (10 g SiO_2; 2% MeOH-$CHCl_3$) of the residue gave 94 mg of the desired product as a yellow foam.

The compound exists as 3:2 mixture of rotamers. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, 1/3H), 8.35 (d, 2/3H), 8.19 (d, 1H), 7.72 (d, 2/3H), 7.60 (d, 1/3H), 7.38 (d, 2/3H), 7.32 (d, 1/3H), 7.22-7.08 (m, 3H), 7.00 (2t, 1H), 6.93 (d, 1/3H), 6.69 (t, 1H), 6.60 (d, 1/3H), 6.56 (d,

2/3H), 6.50 (d, 2/3H), 5.30-5.15 (m, 1H), 5.00 (bs, 1H), 4.34 (m, 1H), 3.62-3.50 (m, 1H), 3.30-3.11 (m, 4H), 2.90 (dt, 1H), 2.40 (dt, 1/3H), 1.70-1.55 (m, 12/3H), 1.34 (s, 2H), 1.31 (s, 4H), 1.28 (s, 1H), 1.31 (s, 9H), 1.20-1.11 (m, 1H), 0.32 (dt, 1/3H)

Step E: N-[1(R)-[(1,2-Dihydro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide dihydrochloride

To 27.5 mg of the intermediate from Step D was added 1.0 mL of methanol and 1.0 mL of concentrated hydrochloric acid and stirred at RT for 1h. The reaction mixture was concentrated, basified with 5 mL of 10% aqueous sodium carbonate solution, and extracted with chloroform (3X5 mL). The combined organics were washed with brine (10 mL), dried over potassium carbonate, filtered, and concentrated to yield a thick oil. Preparative TLC (0.50 mm plate; chloroform-methanol 96:5+1% NH_4OH) gave 12 mg of the desired product as a yellow solid.

The compound exists as 3:2 mixture of rotamers. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, 1/3H), 8.35 (d, 2/3H), 8.19 (d, 1H), 7.72 (d, 2/3H), 7.60 (d, 1/3H), 7.38 (d, 2/3H), 7.32 (d, 1/3H), 7.22-7.08 (m, 3H), 7.00 (2t, 1H), 6.93 (d, 1/3H), 6.69 (t, 1H), 6.60 (d, 1/3H), 6.56 (d, 2/3H), 6.50 (d, 2/3H), 5.30-5.15 (m, 1H), 4.34 (m, 1H), 3.62-3.50 (m, 1H), 3.30-3.11 (m, 4H), 2.90 (dt, 1H), 2.40 (dt, 1/3H), 1.70-1.55 (m, 12/3H), 1.34 (s, 2H), 1.31 (s, 4H), 1.28 (s, 1H), 1.20-1.11 (m, 1H), 0.32 (dt, 1/3H).

EXAMPLE 22

N-[1(R)-[(1,2-Dihydro-1-methylcarbonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

To 26 mg of the intermediate from Example 21, Step D in 1.0 mL of 1,2-dichloroethane and 55 μL (0.14 mmol) of N-methyl-morpholine at 0°C was added 6.6 μL (0.93 mmol) of acetyl chloride and stirred for 1h. The reaction mixture was diluted with 5 mL of ether.

washed with 5 mL of 10% aqueous citric acid, 5 mL of saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to give a pale yellow foam which was used without purification.

To the above material in 1.0 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and stirred at RT for 1h. The reaction mixture was concentrated, basified with 5 mL of 10% aqueous sodium carbonate solution, and extracted with chloroform (3X5 mL). The combined organics were washed with brine (10 mL), dried over potassium carbonate, filtered, and concentrated to yield a thick oil. To a solution of this material in 1.0 mL of methanol was added 1.0 mL of 4M hydrochloric acid in dioxane and concentrated to dryness to yield 16 mg of the title compound as a pale yellow solid.

The compound exists as a 3:2 mixture of rotamers. ^{1}H NMR (CD_3OD, 400MHz) δ 8.43 (d, 1H), 8.35 (t, 1H), 7.72 (d, 2/3H), 7.61 (d, 1/3H), 7.40-7.25 (m, 2H), 7.20-7.08 (m, 3H), 7.05-6.95 (m, 2 2/3H), 6.50 (d, 1/3H), 5.25-5.10 (m, 1H), 5.00-4.84 (2bd, 1H), 3.68-3.45 (m, 3H), 3.20 (m, 2H), 2.60-2.48 (m, 1 1/3H), 2.30 (dt, 1/3H), 2.00 (s, 1H), 1.98 (s, 2H), 1.81-1.40 (m, 4H), 1.35 (s, 2H), 1.33 (s, 2H), 1.32 (s, 1H), 1.30 (s, 1H), 1.25-1.15 (m, 1H), 1.10-1.00 (m, 1H), 0.20 (dt, 1/3H)

EXAMPLE 23

N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide

To 26 mg (0.050 mmol) of the intermediate from Example 21, Step D in 1.0 ml of 1,2-dichloroethane and 5 µl of N-methyl morpholine was added at 0°C 7.5 µL of benzenesulfonyl chloride and stirred for 1h. The reaction mixture was diluted with 10 ml of ether washed with 5 ml of 10% aqueous citric acid, 5 ml of saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 29.8 mg of a crude product as a pale yellow foam. To a solution of this material in 2 ml of methanol was added 1.0 ml of conc. hydrochloric acid and stirred for 1h. The solvent were

removed under reduced pressure to yield the title compound as a brown solid.

This compound exists as a 3:2 mixture of rotamers. ^{1}H NMR($CDCl_3$, 400MHz) δ 8.30 (bs, 1/3H), 8.20 (bs, 2/3H), 8.05 (bs, 2/3H), 7.88 (d, 1/3H), 7.72-7.45 (m, 5H), 7.43-7.30 (m, 4H), 7.20-7.05 (m, 2H), 7.00-6.90 (m, 2$^{2/3}$H), 6.35 (d, 1/3H), 5.25-5.10 (m, 1H), 4.90 (bs, 1H), 4.30 (dt, 1H), 4.15 (dt, 1H), 3.95 (dd, 1H), 3.60-3.40 (m, 3H), 3.25-3.20 (m, 2H), 2.90 (dt, 1H), 2.73 (dt, 2$^{2/3}$H), 2.35 (m, 1$^{1/3}$H), 1.80 (m, 1H), 1.50 (s, 1H), 1.43 (s, 2H), 1.39 (s, 3H), 1.30-1.20 (m, 2H), 1.00 (bd, 1/3H), 0.90-0.70 (m, 2H), 0.55 (bd, 1/3H), 0.48 (dd, 2/3H), -0.90 (dt, 1/3H)

EXAMPLE 24

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide hydrochloride

To a solution of 0.258 g (0.50 mmol) of the intermediate from Example 21, Step D in 10 mL of dry dichloromethane at 0°C was added 0.39 mL(1.00 mmol) of N-methyl morpholine, and 45 μL (0.60 mmol) of methanesulfonyl chloride and stirred for 30 min. The reaction was diluted with 10 mL of ether and washed with saturated sodium bicarbonate solution (5 mL), brine (5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to yield the product as a pale yellow foam which was used without purification. To a solution of this material in 3.0 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and stirred at RT for 1h. The reaction mixture was concentrated, basified with 5 mL of 10% aqueous sodium carbonate solution, and extracted with chloroform (3X5 mL). The combined organics were washed with brine(10 mL), dried over potassium carbonate, filtered, and concentrated to yield a thick oil. To a solution of this material in 3.0 mL of methanol was added 200 μL of 4M hydrochloric acid in dioxane and concentrated to dryness to yield 98 mg of the desired material as a pale yellow solid.

The compound exists as a 3:2 mixture of rotamers. ^1H NMR (CD_3OD, 400MHz) δ 8.43 (d, 1H), 8.35 (t, 1H), 7.72 (d, 2/3H), 7.61 (d, 1/3H), 7.40-7.25 (m, 2H), 7.20-7.08 (m, 3H), 7.05-6.95 (m, 2 2/3H), 6.50 (d, 1/3H), 5.25-5.10 (m, 1H), 5.00-4.84 (2bd, 1H), 3.68-3.45 (m, 3H), 3.20 (m, 2H), 2.82 (s, 1H), 2.80 (s, 2H), 2.60-2.48 (m, 1 1/3H), 2.30 (dt, 1/3H), 1.81-1.40 (m, 4H), 1.35 (s, 2H), 1.33 (s, 2H), 1.32 (s, 1H), 1.30 (s, 1H), 1.25-1.15 (m, 1H), 1.10-1.00 (m, 1H), 0.20 (dt, 1/3H)

EXAMPLE 25

N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-[3-phenylpropyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-[(1,1-dimethylethoxy)carbonyl]amino-2-methylpropanamide

The title compound was prepared from (2R)-2-[(1,1-dimethylethoxy)carbonyl]amino-4-phenyl-1-butanoic acid and 1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidine] hydrochloride by using the coupling method as described in Example 18, Step B. The crude product was purified on silica gel using 5% Acetone in CH_2Cl_2.

^1H NMR (400MHz, $CDCl_3$) δ 7.2 (m, 9H), 4.9 (m, 1H), 4.5 (m, 1H), 3.8 (m, 2H), 3.2 (m, 2H), 2.9 (s, 3H), 2.7 (m, 2H), 2.3 (s, 2H), 2.0 (m, 2H), 1.7 (m, 4H), 1.5 (s, 6H), 1.4 (s, 9H).

Step B: N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methylpropanamide hydrochloride

Prepared from the intermediate obtained in step A using the deprotection method as described in Example 18, Step C.

^{1}H NMR (400MHz, CD_3OD) δ 7.3 (m, 9H), 4.5 (m, 1H), 3.9 (m, 2H), 3.5 (m, 2H), 3.2 (m, 2H), 2.9 (s, 3H), 2.7 (m, 4H), 2.0 (m, 4H), 1.6 (s, 6H).

EXAMPLE 26

N-[1(R)-[(1,2-Dihydro-1-trifluoromethanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: 1,2-Dihydro-1-benzyloxycarbonyl--5-fluoro-spiro[3H-indole-3,4'-piperdine]

To 7.82 g of 60% sodium hydride was added hexane and the liquids were decanted. To this was added a solution of 11.10 mL(89 mmol) of 2,5-difluorophenylacetonitrile in 150 mL of DMSO and stirred for 30 min. A solution of 15.10 g of 1-chloromethyl ethylamine hydrochloride in 150 mL of DMSO was added dropwise and heated at 75°C for 4h. The reaction mixture was poured into 600 g of ice and extracted with ether (5X200 mL). The combined organics were washed with 3X100 mL of 2N hydrochloric acid. The combined aqueous extracts were basified to pH=9 with 50% aqueous sodium hydroxide and extracted with ether (3X200 mL). The combined organics were washed with brine (100 mL), dried over potassium carbonate and concentrated to give 15.54 g of a thick oil.

Ethanol (24 mL) was added in dropwise fashion to 9.90 g of lithium aluminum hydride in 250 mL of DME at 0°C and then warmed to reflux. A solution of the compound in 250 mL of DME was added and refluxed for 72h. The reaction was then cooled to 0°C and quenched with water (10 mL), 10 mL of 15% NaOH, and 30mL of water. The slurry was dried over K_2CO_3, filtered, and concentrated to give 13.6 g of a thick oil. This crude product was triturated with hexanes, the solid was filtered, and washed further with hexanes. 200MHz NMR ($CDCl_3$) of the solid (2.6 g) indicated about 75% of the desired spiro-indoline.

To a solution of 1.02 g of this mixture in 50 mL of CH_2Cl_2 at 0°C was added 1.0 mL of triethylamine and 0.80 mL of CBZ-Cl and stirred for 1h at RT. The reaction mixture was poured into 50 mL of 5% HCl and the aqueous layer was separated. The aqueous layer was basified with 50% NaOH to pH=10 and extracted with CH_2Cl_2 (3x25 mL). The combined organics were washed with brine (50 mL), dried over K_2CO_3, and concentrated to yield 1.26 g of the compound as a thick oil.

^{1}H NMR (200MHz, $CDCl_3$) δ 7.7-7.90 (m, 1H), 7.50-7.15 (m, 6H), 6.95-6.60 (m, 2H), 5.28 (bs, 2H), 3.90 (bs, 2H), 2.85 (bd, 2H), 2.30 (s, 3H), 2.20-1.80 (m, 4H), 1.65 (bd, 2H).

Step B: N-[1(R)-[(1,2-Dihydro-1-benzyloxycarbonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

To 1.62 g (4.62 mmol) of the above intermediate from Step A in 10 mL of 1,2-dichloroethane at 0°C was added 0.65 mL of ACE-Cl and refluxed for 1h. The reaction mixture was concentrated to one-third the volume and diluted with 10 mL of methanol and heated to reflux for 1h. The reaction mixture was concentrated to dryness and triturated with ether to give brown solid. This material was dissolved in saturated sodium bicarbonate solution (25 mL), and extracted with dichloromethane (2X25 mL). The combined organics were dried over K_2CO_3 and concentrated to give 0.384 g of the free base.

To 0.384 g of this material in 15 mL of CH_2Cl_2 was added 0.483 g of the acid intermediate obtained from Step C of Example 21, 0.189 g of HOBT, and 0.34 g of EDC and stirred for 18h. The reaction mictured was poured into 10 mL of water and extracted with CH_2Cl_2 (2X10 mL). The combined organics were washed with 20 mL of 10% citric acid, 20 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatographed of the residue on 25 g of silica gel with hexanes-acetone (1:1) as eluent gave 0.389 g of the desired material.

^{1}H NMR (200MHz, $CDCl_3$) δ 7.7-7.90 (m, 1H), 7.50-7.15 (m, 6H), 6.95-6.60 (m, 2H), 5.28 (bs, 2H), 3.90 (bs, 2H), 2.85 (bd, 2H), 2.30 (s, 3H), 2.20-1.80 (m, 4H), 1.65 (bd, 2H).

Step C: N-[1(R)-[(1,2-Dihydro-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

To a solution of 0.363 g of the intermediate obtained from Step B in 5 mL of of ethanol was added 0.10g of 20% palladium hydroxide on carbon and hydrogenated under H_2 balloon for 1h. the catalyst was filtered off and washed with more methanol. The filtrate was concentrated to yield 0.262 g of the desired material.

^{1}H NMR (400MHz, $CDCl_3$) This material was 2:1 mixture of rotamers. δ 8.85-8.60 (2bs, 1H), 7.70(d, 2/3H), 7.55 (d, 1/3H), 7.38 (d, 2/3H), 7.30 (d, 1/3H), 7.28-7.15 (m, 4H), 7.13-7.02 (m, 2H), 6.65 (dt, 2H), 6.50 (dd, 1/3H), 6.45 (dd, 2/3H), 6.14 (dd, 2/3H), 5.30-5.13 (m, 1H), 5.10 (bs, 1H), 4.30 (bd, 2/3H), 422 (bd, 1/3H), 3.50-3.30 (m, 1H), 3.30-3.00 (m, 4H), 3.00-2.80 (m, 1H), 2.73 (t, 1H), 2.53-2.40 (m, 11/3H), 2.20 (t, 1/3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.41 (s, 9H) 1.20 (dt, 1/3H), 0.95 (bd, 2/3H), 0.90 (dt, 2/3H), -0.05 (dt, 1/3H).

Step D: N-[1(R)-[(1,2-Dihydro-1-trifluoromethanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

To a solution of 30 mg of the intermediate obtained from Step C in 1mL of dichloromethane at 0°C was added 0.050 mL of triethylamine and 0.020 mL of triflic anhydride and stirred for 5 min. the catalyst was filtered off and washed with more methanol. The reaction was poured into 5 mL of 5% aqueous sodium carbonate solution and stirred for 5 min. The aqueous layer was extracted with CH_2Cl_2 (2X5 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the residue on 3 g of silica gel with CH_2Cl_2-acetone (4:1) as eluent gave 21 mg of product.

^1H NMR (400MHz, $CDCl_3$) This material was 2:1 mixture of rotamers. δ 8.40 (bs, 2/3H), 8.25 (bs, 1/3H), 7.70(d, 2/3H), 7.60 (d, 1/3H), 7.40 (d, 2/3H), 7.35-7.10 (m, 5H), 6.90-6.80 (m, 2H), 6.18 (dd, 1H), 5.30-5.13 (m, 1H), 4.95(bs, 2/3H), 4.90 (s, 1/3H), 4.45 (bd, 2/3H), 4.35 (bd, 1/3H), 385-3.70 (m, 2H), 3.70-3.55 (m, 2H), 3.30-3.10 (m, 2H), 2.70 (t, 1H), 2.45 (t, 1/3H), 2.35 (t, 2/3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.41 (s, 9H), 1.20 (dt, 1/3H), 0.95 (bd, 2/3H), 0.90 (dt, 2/3H), -0.05 (dt, 1/3H).

Step E: N-[1(R)-[(1,2-Dihydro-1-trifluoromethanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]--2-methylpropanamide trifluoroacetate

To a solution of 21 mg of the intermediate obtained from Step D was maintained in 1 mL of dichloromethane and 1 mL of trifluoroacetic acid at room temperature for 30 min. The volatiles were evaporated to dryness and triturated with ether to give a yellow solid. ^1H NMR (400MHz, CD_3OD) This material was 2:1 mixture of rotamers. δ 7.65(d, 2/3H), 7.60 (d, 1/3H), 7.42 (d, 2/3H), 7.35-7.10 (m, 5H), 6.93-6.80 (m, 2H), 6.24 (dd, 1H), 5.30-5.13 (m, 1H), 4.95(bs, 2/3H), 4.90 (s, 1/3H), 4.45 (bd, 2/3H), 4.35 (bd, 1/3H), 385-3.70 (m, 2H), 3.70-3.55 (m, 2H), 3.30-3.10 (m, 2H), 2.70 (t, 1H), 2.45 (t, 1/3H), 2.35 (t, 2/3H), 1.49 (s, 3H), 1.45 (s, 3H), 0.93 (bd, 2/3H), 0.90 (dt, 2/3H), -0.05 (dt, 1/3H).

EXAMPLE 27

N-[1(R)-[(1,2-Dihydro-1-[methoxycarbonyl]methylsulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: N-[1(R)-[(1,2-Dihydro-1-[methoxycarbonyl]methyl-sulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]--2-methylpropanamide trifluoroacetate

To a solution of 77 mg of the intermediate obtained from Step C of Example 26 in 1 mL of dichloromethane at 0°C was added 0.30 mL of N-methylmorpholine, and 0.024 mL of 2-carbomethoxy-methanesulfonylchloride and stirred for 1h. The reaction was poured into 5 mL of 5% aqueous sodium carbonate solution and stirred for 5 min. The aqueous layer was extracted with CH_2Cl_2 (2X5mL) and the combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the residue on 5g of silica gel with CH_2Cl_2-acetone (4:1) as eluent gave 64 mg of product. ^{1}H NMR (400MHz, $CDCl_3$) This material was 2:1 mixture of rotamers. δ 8.48 (bs, 2/3H), 8.35 (bs, 1/3H), 7.70(d, 2/3H), 7.60 (d, 1/3H), 7.40 (d, 2/3H), 7.32 (d, 1/3H), 7.25-7.00 (m, 4H), 6.90-6.78 (m, 2H), 6.18 (dd, 1H), 5.30-5.20 (m, 1H), 4.97(bs, 2/3H), 4.91 (s, 1/3H), 4.50-4.35 (2bd, 1H), 4.02 (s, 2/3H), 3.99 (s, 1/3H), 3.76(q, 2H), 3.58 (s, 1H), 3.56 (s, 2H), 3.08-3.07 (m, 2H), 2.72 (t, 1H), 2.50-2.30 (2t, 1H), 1.65 (t, 1/3H), 1.50 (s, 2H), 1.46 (s, 4H), 1.40 (s, 9H), 1.30 (m, 1/3H), 1.10 (bd, 2/3H), 0.88 (dt, 2/3H), -0.13 (dt, 1/3H).

<u>Step B:</u> <u>N-[1(R)-[(1,2-Dihydro-1-[methoxycarbonyl]methyl-sulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-methylpropanamide trifluoroacetate</u>

To a solution of 24 mg of the intermediate obtained from Step A was maintained in 1 mL of dichloromethane and 1 mL of trifluoroacetic acid at room temperature for 30 min. The volatiles were evaporated to dryness and triturated with ether to give 23 mg of a colorless solid.

^{1}H NMR (400MHz, CD_3OD) This material was 2:1 mixture of rotamers. δ 8.70 (bs, 1/3H), 8.60 (bs, 2/3H), 7.60(m, 2/3H), 7.50 (d, 2/3H), 7.48 (m, 1/3H), 7.40 (d, 2/3H), 7.31 (d, 1/3H), 7.25-7.00 (m, 4H), 6.95-6.85 (m, 1H), 6.70 (dd, 1/3H), 6.15 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.38 (bd, 1/3H), 4.28 (bd, 2/3H), 4.02 (s, 2/3H), 3.99 (s, 1/3H), 3.76(q, 2H), 3.58 (s, 1H), 3.56 (s, 2H), 3.08-3.07 (m, 2H), 2.72 (t, 1H),

2.50-2.30 (2t, 1H), 1.65 (t, 1/3H), 1.65 (s, 2H), 1.60 (s, 4H), 1.30 (m, 1/3H), 1.00 (bd, 2/3H), 0.88 (dt, 2/3H), -0.10 (dt, 1/3H).

EXAMPLE 28

N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R)-[(1,2-Dihydro-1-benzyloxycarbonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

To 0.330 g of the 1,2-Dihydro-1-benzyloxycarbonyl-5-fluoro-spiro[3H-indole-3,4'-piperdine] obtained from Step A of Example 26 in 10 mL of 1,2-dichloromethane at room temperature was added 0.35 g of N-tBOC-O-benzyl-D-serine, 0.195 g of HOBT, and 0.30 g of EDC and stirred for 18h. The reaction mictured was poured into 10mL of water and extracted with CH_2Cl_2 (2X10 mL). The combined organics were washed with 20 mL of 10% citric acid, 20 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated.

To a solution of the intermediate obtained from Step A in 5 mL of CH_2Cl_2 was added 5 mL of trifluoroacetic acid and stirred at RT for 30 min. The reaction mixture was concentrated, diluted with 5.0 mL of dichloromethane and carefully basified with 10 mL of 10% aqueous sodium carbonate solution. The organic layer was separated and the aqueous layer was further extracted with 2X15 mL of dichloromethane. The combined organics were washed with 5 mL of water, dried over potassium carbonate, filtered and concentrated to give 0.39 g of the amine as a thick oil.

To 0.39 g of the above intermediate in 10 mL of 1,2-dichloromethane at room temperature was added 0.24 g of N-tBOC-α-methylalanine, 0.195 g of HOBT, and 0.30 g of EDC and stirred for 18h. The reaction mixtured was poured into 10 mL of water and

extracted with CH_2Cl_2 (2X10 mL). The combined organics were washed with 20 mL of 10% citric acid, 20 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatography of the residue over 30 g of silica gel with hexane-ethyl acetate (2:1) as eluent gave 0.33 g of product
^{1}H NMR (200MHz, $CDCl_3$) δ 7.80(bs, 1H), 7.50-7.15 (m, 5H), 7.10(bd, 1H), 6.90-6.70(m, 1H), 6.27 (bd, 1H), 7.35-7.10 (m, 5H), 5.35-5.10 (m, 3H), 4.99 (s, 1H), 4.70-4.40 (m, 3H), 3.90-3.50 (m, 4H), 3.15-2.90 (m, 2H), 2.80-2.50 (m, 2H), 1.80-1.40 (m, 2H), 1.50 (3H), 1.42 (s, 6H).

<u>Step B:</u> <u>N-[1(R)-[(1,2-Dihydro-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide</u>

To a solution of 0.330 g of the intermediate obtained from Step A in 5 mL of ethanol at was added 1 drop of triethylamine and hydrogenated with hydrogen balloon for 3h. The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give 0.269 g of the product as a colorless foam.
^{1}H NMR (400MHz, $CDCl_3$) δ 7.35-7.20 (m, 4H), 7.17-7.08 (m, 2H), 6.80-6.65 (m, 2/2/3H), 6.27 (dt, 1/3H), 5.20-5.10 (m, 1H), 4.90 (s, 1H), 4.60-4.40 (m, 3H), 4.00 (bt, 1H), 3.75-3.60 (m, 1H), 3.55-3.40 (m, 3H), 3.18-3.30 (m, 2H), 2.90-2.65 (m, 1H), 1.83-1.50 (m, 4H), 1.48 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

<u>Step C:</u> <u>N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenyl-methyloxy)ethyl]-[[(1,1-dimethylethyloxy)carbonyl]-amino]-2-methylpropanamide</u>

To a solution of 0.134 g the intermediate from Step B in 5 mL of dichloromethane was added 0.080 mL of N-methylmorpholine, and 0.022 mL of methanesulfonylchloride and stirred at 0°C for 30 min. The reaction mixture was diluted with an additional 5 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate solution, brine (5 mL), dried over MgSO4 and concentrated. Flash

chromatography of the residue over 20 g of silica gel gave 0.101 g of the desired product.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 7.08 (d, 1H), 6.95-6.80 (m, 2/1/3H), 6.23 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.90 (bs, 1H), 4.60 (bd, 2/3H), 4.58-4.40 (m, 3/1/3H), 4.10-4.00 (m, 1H), 3.388-3.70 (m, 21/3H), 3.66-3.60 (m, 1/2H), 3.60-3.50 (m, 1H), 3.10-2.95 (m, 1H), 2.86 (s, 1H), 2.84 (s, 2H), 2.80 (t, 1/3H), 2.65 (t, 2/3H), 2.90-2.50 (m, 4H), 1.45 (s, 4H), 1.44 (s, 2H), 1.42 (s, 3H), 1.40 (s, 6H).

Step D: N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenyl-methyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of 0.101 g the intermediate from Step C in 1mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (10 mL), and extracted with dichloromethane (3X5 mL). The combined organics were washed with brine (5 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.10 mL of 4M HCl in EtOAc was added at 0°C. The precipitate was filtered under nitogen and washed with EtOAc/ether (1:1) and dried to give 62 mg of the product as a white solid.

1H NMR (400MHz, CD_3OD) δ 7.40-7.20 (m, 5H), 7.08 (d,1H), 6.95-6.80 (m, 2/1/3H), 6.23 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.60 (bd, 2/3H), 4.58-4.40 (m, 3/1/3H), 4.10-4.00 (m, 1H), 3.388-3.70 (m, 21/3H), 3.66-3.60 (m, 1/2H), 3.60-3.50 (m, 1H), 3.10-2.95 (m, 1H), 2.86 (s, 1H), 2.84 (s, 2H), 2.80 (t, 1/3H), 2.65 (t, 2/3H), 2.90-2.50 (m, 4H), 1.45 (s, 4H), 1.44 (s, 2H).

EXAMPLE 29

Step A: N-[1(R)-[(1,2-Dihydro-1-benzenesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-

(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

To a solution of 0.026 g the intermediate from Step B of Example 27 in 2 mL of dichloromethane was added 0.020 mL of N-methylmorpholine, and 0.012 mL of benzeneesulfonylchloride and stirred at 0°C for 1h. The reaction mixture was poured into 10 mL of ether and washed with 5 mL of saturated sodium bicarbonate solution, dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica gel with CH_2Cl_2-ether (2:1) as eluent gave 0.019 g of the product.

This material was treated with 1 mL of dichloromethane and 1 mL of trifluoroacetic acid for 1h. The reaction mixture was evaporated to dryness and the residue was triturated with ether to give 18 mg of the desired product as a white solid.

^1H NMR (400MHz, CD_3OD) δ 7.80 (d, 2H), 7.70-7.55 (m, 2H), 7.55-7.50 (m, 2H), 7.40-7.20 (m, 42/3H), 7.03-6.92 (m, 1H), 6.82 (dt, 2/3H), 6.47 (dt, 2/3H), 5.08 (dt, 1H), 4.60-4.48 (m, 2H), 4.33 (bt, 1H), 3.94-3.85 (m, 3H), 3.75-3.65 (m, 2H), 3.10 (dt, 1H), 2.80 (dt, 1H), 1.73 (dt, 1H), 1.58 (s, 4H), 1.56 (s, 2H), 1.50 (dt, 1H), 1.38 (dt, 1H), 1.10 (dt, 2H).

EXAMPLE 30

N-[1(R)-[(1,2-Dihydro-1-ethanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R)-[(1,2-Dihydro-1-benzyloxycarbonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)-ethyl]-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

To 5 g of the 1,2-Dihydro-1-benzyloxycarbonyl-spiro[3H-indole-3,4'-piperdine] hydrochloride in 100 mL of dichloromethane at room temperature was added 3.64 g of N-tBOC-O-benzyl-D-serine, 1.83 g of HOBT, 2.60 mL of N-methylmorpholine, and 3.70 g of EDC and stirred for 18h. The reaction mixture was poured into 100 mL of water and extracted with CH_2Cl_2 (2X100 mL). The combined organics were washed with 100 mL of 10% citric acid, 100 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated.

To a solution of the intermediate obtained from Step A in 20 mL of CH_2Cl_2 was added 20 mL of trifluoroacetic acid and stirred at RT for 30 min. The reaction mixture was concentrated, diluted with 50 mL of dichloromethane and carefully basified with 100 mL of 10% aqueous sodium carbonate solution. The organic layer was separated and the aqueous layer was further extracted with 2X50 mL of dichloromethane. The combined organics were washed with 50 mL of water, dried over potassium carbonate, filtered and concentrated to give the amine as a thick oil.

To the above intermediate in 50 mL of dichloromethane at room temperature was added 2.50 g of N-tBOC-α-methylalanine, 1.83 g of HOBT, and 3.70 g of EDC and stirred for 18h. The reaction mixtured was poured into 10 mL of water and extracted with CH_2Cl_2 (2X10 mL). The combined organics were washed with 20 mL of 10% citric acid, 20 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatography of the residue over 300g of silica gel with hexane-ethyl acetate (2:1) as eluent gave 8.1 g of product
^{1}H NMR (400MHz, $CDCl_3$) δ 7.85(bs, 1H), 7.45-7.20 (m, 10H), 7.20-7.05 (m, 22/3H), 6.95 (t, 1/3H), 6.88(t, 1/3H), 6.53 (dd, 2/3H), 5.35-5.20 (m, 2H), 5.20-5.10 (m, 1H), 4.92 (bs, 1H), 4.65-4.20 (m, 4H), 4.05 (bd, 2/3H), 4.00-3.80 (m, 1,1/3H), 3.80-3.60 (m, 1H), 3.10 (t, 2/3H), 3.00-2.85 (m, 1/3H), 2.82-2.60 (2t, 1H), 1.90-1.55 (m, 5H), 1.49 (s, 4H), 1.42 (s, 2H), 1.40 (s, 9H).

<u>Step B:</u> <u>N-[1(R)-[(1,2-Dihydro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethyl-ethoxy)carbonyl]amino]-2-methylpropanamide</u>

To a solution of 8.10 g of the intermediate obtained from Step A in 80 mL of ethanol was added 1 g of 20% palladium hydroxide/C and hydrogenated with hydrogen balloon for 1h. The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give 4.69 g of the product as a colorless foam.
^{1}H NMR (400MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 7.18 (d, 1/2H), 7.10 (d, 1/2H), 7.04-6.98 (m, 2H), 6.75-6.60 (m, 2H), 5.20-5.10 (m, 1H), 4.97 (bs, 1H), 4.55-4.40 (m, 3H), 3.95 (dd, 1H), 3.73-3.61 (m, 1H), 3.60-3.50 (m, 1H), 3.50-3.33 (m, 3H), 3.10 (dt, 1H), 2.83 (dt, 1H), 1.85-1.55 9m, 5H), 1.47 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

<u>Step C:</u> <u>N-[1(R)-[(1,2-Dihydro-1-ethanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)-ethyl]-2-amino-2-methylpropanamide</u>

To a solution of 0.158 g the intermediate from Step B in 5 mL of dichloromethane was added 0.053 mL of N-methylmorpholine, and 0.034 mL of ethanesulfonylchloride and stirred at 0°C for 30 min and RT for 1h. The reaction mixture was diluted with an additional 5 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate solution, brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica gel with CH_2Cl_2-ether (3:1) as eluent gave 0.057 g of the desired product.

To a solution of 0.057 g the above intermediate in 1 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was concentrated to dryness and triturated with ether to give 0.034 g of the product as a yellow solid.

^1H NMR (400MHz, CD_3OD) δ 7.40-7.25(m, 5H), 7.25-7.13 (m, 21/2H), 7.03 (t, 1/2H), 6.95 (t, 1/2H), 6.80 (d, 1/2H), 5.18 (dt, 1H), 4.60-4.42 (m, 3H), 4.08 (t, 1H), 3.96 (s, 2H), 3.83-3.70 (m, 2H), 3.29-3.15 (m, 3H), 2.84 (dt, 1H), 1.90 (dt, 1H), 1.74-1.62 (m, 4H), 1.62 (s, 2H), 1.60 (s, 4H), 1.33 (dt, 3H).

EXAMPLE 31

Step A: N-[1(R)-[(1,2-Dihydro-1-[2-methyl-2-propanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide

To a solution of 0.212 g the intermediate from Step B of Example 29 in 2 mL of 1,2-dichloroethane was added 0.083 mL of triethylamine, and 0.054 mL of isopropylsulfonylchloride and stirred at 0°C for 30 min and at RT for 3h. The reaction mixture was diluted with a 5 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate solution, brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica

gel with CH_2Cl_2-ether (3:1) as eluent gave 0.113 g of the desired product.

To a solution of 0.101 g the above intermediate in 1 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (10 mL), and extracted with dichloromethane (3X5 mL). The combined organics were washed with brine (5 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.10 mL of 4M HCl in EtOAc was added at 0°C. The precipitate was filtered under nitogen and washed with EtOAc/ether (1:1) and dried to give 88 mg of the product as a white solid.
^{1}H NMR (400MHz, CD_3OD) δ 7.40-7.20 (m, 5H), 7.08 (d,1H), 6.95-6.80 (m, 2/1/3H), 6.23 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.60 (bd, 2/3H), 4.58-4.40 (m, 3/1/3H), 4.10-4.00 (m, 1H), 3.388-3.70 (m, 21/3H), 3.66-3.60 (m, 1/2H), 3.60-3.50 (m, 1H), 3.10-2.95 (m, 1H), 2.86 (s, 1H), 2.84 (s, 2H), 2.80 (t, 1/3H), 2.65 (t, 2/3H), 2.90-2.50 (m, 4H), 1.45 (s, 4H), 1.44 (s, 2H).

EXAMPLE 32

Step A: N-[1(R)-[(1,2-Dihydro-1-[2-carbomethoxymethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]-amino]-2-methylpropanamide hydrochloride

To a solution of 0.50 g the intermediate from Step B of Example 29 in 10 mL of dichloromethane was added 0.21 mL of N-methylmorpholine and 0.10 mL of 2-carbomethoxymethanesulfonyl-chloride and stirred at 0°C for 30 min. The reaction mixture was diluted with 10 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate solution, brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 20 g of silica gel with CH_2Cl_2-ether (3:1) as eluent gave 0.529 g of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.20 (m, 5H), 7.20-7.10 (m, 21/2H), 7.08 (dt, 1H), 6.92 (t, 1/2H), 6.55 (d, 1/2H), 5.20-5.10 (m, 1H), 4.94 (bs, 1H), 4.60 (bd, 1H), 4.53-4.40 (m, 2H), 4.10 (2bs, 2H), 4.05-3.90 (m, 2H), 3.70 (dt, 1H), 3.63 (s, 11/2H), 3.61 (s, 11/2H), 3.59-3.50 (m, 1H), 3.05 (dt, 1H), 2.70 (dt, 1H0, 1.90-1.50 (m, 4H), 1.49 (s, 4H), 1.44 (s, 2H), 1.39 (s, 9H).

Step B: N-[1(R)-[(1,2-Dihydro-1-[2-carbomethoxymethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of 0.113 g the above intermediate in 1 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (10 mL), and extracted with dichloromethane (3X5 mL). The combined organics were washed with brine (10 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.20 mL of 4M HCl in EtOAc was added at 0°C. Ether was added and the precipitate was filtered under nitogen and washed with ether and dried to give 0.108 g of the product as a white solid.
^{1}H NMR (400MHz, CD_3OD) δ 7.40-7.20 (m, 5H), 7.08 (d,1H), 6.95-6.80 (m, 2/1/3H), 6.23 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.60 (bd, 2/3H), 4.58-4.40 (m, 3/1/3H), 4.10-4.00 (m, 1H), 3.388-3.70 (m, 21/3H), 3.66-3.60 (m, 1/2H), 3.60-3.50 (m, 1H), 3.10-2.95 (m, 1H), 2.86 (s, 1H), 2.84 (s, 2H), 2.80 (t, 1/3H), 2.65 (t, 2/3H), 2.90-2.50 (m, 4H), 1.45 (s, 4H), 1.44 (s, 2H).

EXAMPLE 33

Step A: N-[1(R)-[(1,2-Dihydro-1-[2-carboxymethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide trifluoroacetate

To a solution of 0.126 g the intermediate from Step A of Example 32 in 3 mL of methanol and 1 mL of water at 0°C was added 2 drops of 5N aqueous sodium hydroxide and stirred for 30 min. The reaction mixture was acidified to pH=2 with 0.50N aqueous hydrochloric acid, diluted with brine (5 mL), and extracted with CH_2Cl_2 (2X5 mL). The combined organics were washed with brine(10 mL), dried over $MgSO_4$ and concentrated to give 0.098 g of a white foam.

^1H NMR (400MHz, $CDCl_3$) δ 9.80 (bs, 1H), 7.45 (d, 1/2H), 7.40-7.13 (m, 7H), 7.02 (t, 1/2H), 6.90 (t, 1/2H), 6.50 (d, 1/2H), 5.22-5.10 (m, 1H), 4.60-4.40 (m, 3H), 4.20-4.00 (m,3H), 3.92 (d, 1H), 3.70-5.50 (m, 2H), 3.04 (dt, 1H), 2.70 (dt, 1H), 1.93-1.50 (m, 4H), 1.42 (s, 6H), 1.33 (s, 9H).

<u>Step B:</u> <u>N-[1(R)-[(1,2-Dihydro-1-[2-carboxymethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide</u>

To a solution of 0.098 g the intermediate from Step A in 1 mL of dichloromethane was added 1 mL of trifluoroacetic acid and stirred for 30 min. The reaction mixture was evaporated to dryness and triturated with ether to 0.096 g of the product as a white solid.

^1H NMR (400MHz, CD_3OD) δ 7.40-7.28 (m, 6H), 7.24-7.15 (m, 21/2H), 7.00 (dt, 1H), 6.80 (d, 1/2H), 5.17 (dt, 1H), 4.60-4.45 (m, 2H), 4.22 (d, 2H), 4.14-4.00 (m, 3H), 3.81-3.70 (m, 2H), 3.22 (dt, 1H), 2.83 (dt, 1H), 1.96 (dt, 1/2H), 1.80-1.64 (m, 41/2H), 1.62 (s, 1H), 1.60 (s, 5H).

<u>EXAMPLE 34</u>

<u>Step A:</u> <u>N-[1(R)-[(1,2-Dihydro-1-[2-hydroxyethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide trifluoroacetate</u>

To a solution of 0.222 g the intermediate from Step A of Example 32 in 2 mL of 2 mL of anhydrous tetrahydrofuran at RT was added was added 0.48 mL of 2M solution of lithium borohydride in tetrahydrofuran and stirred for 3h. The reaction mixture was quenched with 0.50 mL of acetone, diluted with 15 mL of water and extracted with CH_2Cl_2 (2X15 mL). The combined organics were washed with brine(10 mL), dried over $MgSO_4$ and concentrated to give 0.27 g of a white foam. Flash chromatography of the residue over 10g of silica gel with CH_2Cl_2-acetone (2:1) as eluent gave 0.129 g of the desired material as a thick oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.32–7.20 (m, 6H), 7.20-7.10 (m, 2H), 7.09 (d, 1/2H), 6.98 (t, 1/2H), 6.90 (t, 1/2H), 6.54 (d, 1/2H), 5.17-5.10 (m, 1H), 5.00 (bs, 1H), 4.61-4.39 (m, 3H), 4.10-3.95 (m, 5H), 3.93-3.74 (m, 2H), 3.66 (ddd, 1H), 3.53 (dt, 1H), 3.27 (dt, 2H), 3.00 (dt, 1H), 2.70 (dt, 1H), 1.90-1.50 (m, 4H), 1.43 (s, 4H), 1.41 (s, 2H), 1.36 (s, 9H).

<u>Step B:</u> <u>N-[1(R)-[(1,2-Dihydro-1-[2-hydroxyethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide trifluoroacetate</u>

To a solution of 0.129 g the intermediate from Step A in 1mL of dichloromethane was added 1 mL of trifluoroacetic acid and stirred for 30 min. The reaction mixture was evaporated to dryness and triturated with ether to 0.113 g of the product as a white solid.

^{1}H NMR (400MHz, CD_3OD) δ 7.40–7.25 (m, 6H), 7.25-7.13 (m, 21/2H), 6.98 (dt, 1H), 6.80 (d, 1/2H), 5.20-5.10 (m, 1H), 4.60-4.43 (m, 3H), 4.10-3.90 (m, 5H), 3.81-3.70 (m, 2H), 3.40-3.33 (dt, 2H), 3.20 (dt, 1H), 3.82 (dt, 1H), 2.00-1.63 (m, 4H), 1.61 (s, 1H), 1.58 (s, 5H).

EXAMPLE 35

Step A: N-[1(R)-[(1,2-Dihydro-1-trifluoromethanemethanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide hydrochloride

To a solution of 0.150 g the intermediate from Step B of Example 29 in 5 mL of dichloromethane was added 0.10 mL of N-methylmorpholine and 0.057 mL of trifluoromethanesulfonic anhydride and stirred at 0°C for 15 min. The reaction mixture was diluted with 5 mL of saturated aqueous sodium bicarbonate solution and extracted with 2X5 mL of dichloromethane. The combined organics were washed with brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica gel with hexane-acetone (3:1) as eluent gave 0.136 g of the desired product.
^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.15 (m, 6H), 7.15-6.93 (m, 21/2H), 6.53 (d, 1/2H), 5.20-5.10 (m, 1H), 4.90 (bs, 1H), 4.70-4.60 (m, 3H), 4.15-3.90 (m, 3H), 3.70 (ddd, 1H), 3.60-3.50 (m, 1H), 3.00 (dt, 1H), 2.70 (dt, 1H), 1.93-1.55 (m, 4H), 1.46 (s, 4H), 1.43 (s, 2H), 1.40 (s, 9H).

Step B: N-[1(R)-[(1,2-Dihydro-1-trifluoromethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of 0.136 g the above intermediate in 1 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (5 mL), and extracted with ethylacetate (2X5 mL). The combined organics were washed with brine (5 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.20 mL of 4M HCl in EtOAc was added at 0°C. Ether was added and

the precipitate was filtered under nitrogen and washed with ether and dried to give 0.94 g of the product as a white solid.

^1H NMR (400 MHz, CD_3OD) δ 7.40-7.15 (m, 6H), 7.15-6.93 (m, 21/2H), 6.53 (d, 1/2H), 5.20-5.10 (m, 1H), 4.90 (bs, 1H), 4.70-4.60 (m, 3H), 4.15-3.90 (m, 3H), 3.70 (ddd, 1H), 3.60-3.50 (m, 1H), 3.00 (dt, 1H), 2.70 (dt, 1H), 1.93-1.55 (m, 4H), 1.46 (s, 4H), 1.43 (s, 2H).

EXAMPLE 36

Step A: N-[1(R)-[(1,2-Dihydro-1-benzenesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of 0.148 g the intermediate from Step B of Example 29 in 3 mL of dichloromethane was added 0.30 mL of N-methylmorpholine and 0.022 mL of benzenesulfonyl chloride and stirred at room temperature for 1h. The reaction mixture was diluted with 10 mL of dichloromethane and washed with 10 mL of saturated aqueous sodium bicarbonate solution, dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica gel with hexane-acetone (3:1) as eluent gave 0.190 g of the desired product.

To a solution of 0.190 g the above intermediate in 3 mL of dichloromethane was added 3 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (5 mL), and extracted with ethylacetate (2X5 mL). The combined organics were washed with brine (5 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.40 mL of 4M HCl in EtOAc was added at 0°C. Ether was added and the precipitate was filtered under nitogen and washed with ether and dried to give 0.136 g of the product as a white solid.

^1H NMR (400MHz, CD_3OD) δ 7.82 (d, 2H), 7.67-7.58 (m, 2H), 7.52 (t, 2H), 7.40-7.20 (m, 6H), 7.10-6.90 (m, 11/2H), 6.68 (d, 1/2H), 5.10 (dt, 1H), 4.53 (ABq, 2H), 4.35 (t, 1H), 4.00-3.80 (m, 3H), 3.75-3.65 (m, 2H), 3.10 (dt, 1H), 2,73 (dt, 1H), 1.75 (dt, 1/2H), 1.48 (m, 11/2H), 1.20-1.05 (m, 2H).

EXAMPLE 37

Step A: N-[1(R)-[(1,2-Dihydro-[1-ureidomethyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

To a solution of 0.148 g the intermediate from Step B of Example 29 in 5 mL of 1,2-dichloroethane was added 0.10 mL of methylisocyanate and stirred at RT for 1h. The reaction mixture was evaporated to dryness. Flash chromatography of the residue over 15 g of silica gel with CH_2Cl_2-acetone (2:1) as eluent gave 0.137 g of the desired product.

This material was treated with 3 mL of dichloromethane and 3 mL of trifluoroacetic acid for 30 min. at RT. The reaction mixture was evaporated to dryness and triturated with ether to give 0.126 g of a pale yellow solid.

^1H NMR (400MHz, CD_3OD) δ 7.82(dd, 1H), 7.42-7.35 (m, 5H), 7.30-7.20 (m, 21/2H), 6.75 (d, 1/2H), 5.19 (dt, 1H), 4.60-4.50 (m, 3H), 4.13 (bd, 1H), 3.90-3.68 (m, 4H), 3.25 (t, 1H), 2.90-2.70 (2s, 4H), 1.98 (dt, 1/2H), 1.85-1.65 (m, 31/2H), 1.62 (s, 2H), 1.59 (s, 4H).

EXAMPLE 38

N-[1(R)-[(1,2-Dihydro-1-[1-methoxycarbonyl-1-methyl-ethanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: 1,2-Dihydro-1-[1-methoxycarbonyl-1-methyl-ethane-sulfonyl]-spiro[3H-indole-3,4'-piperdine]

To 5.06 g of 1,2-Dihydro-1-benzyloxycarbonyl-spiro[3H-indole-3,4'-piperdine] hydrochloride in 50 mL of dichloromethane was added 3.0 mL of triethylamine and 3.40 g of di-t-butylcarbonate and stirred at room temperature for 3h. The reaction mixture evaporated to dryness and diluted with 100 mL of ether and washed with 50 mL of 0.50N aqueous hydrochloric acid, 50 mL of brine, dried over $MgSO_4$ and concentrated. To this crude product in 50 mL of ethanol was added 1g of 20% palladium hydroxide on carbon and hydrogenated with H_2 balloon overnight. To 0.506 g of this compound in 15 mL of dichloromethane at 0°C was added 0.74 mL of triethylamine and 0.41 mL of carbomethoxymethanesulfonyl chloride and stirred for 1h. The reaction mixture was diluted with 25 mL of ether and washed with saturated sodium bicarbonate solution (20 mL), dried over $MgSO_4$, and concentrated. Flash chromatography of the residue over 25 g of silica gel with hexane-ethyl acetate 4:1 as eluent gave 1.79 g of the desired material as a thick oil.

Sodium hydride (0.102 g of 60% in mineral oil) was washed with hexanes and then suspended in 5 mL of dry DMF. A solution of 0.158 g of the above intermediate in 1 mL of DMF was added and stirred for 30 min. Methyl iodide (1.85 mmol) was added and stirred for 3h. The reaction mixture was poured into 15 mL of saturated aqueous ammonium chloride solution and extracted with ether (2X15 mL). The combined organics were washed with water (15 mL), brine (15 mL), dried over $MgSO_4$ and concentrated to give 0.179 g of the desired material.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32 (d, 1H), 7.20-6.90 (m, 3H), 4.13 (bd, 2H), 2.83 (bt, 2H), 1.85-1.70 (m, 4H), 1.69 (s, 6H), 148 (s, 9H).

Step B: N-[1(R)-[(1,2-Dihydro-[1-methoxycarbonyl-1-methyl-ethanesulfonyl]-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide

To a solution of 0.179 g of the intermediate from Step A was added 1 mL of dichloromethane and 1 mL of trifluoroacetic acid

and stirred for 30 min. The reaction mixture was evaporated to dryness, basified with 10 mL of 10% aqueous sodium carbonate solution and extracted with 2X10 mL of dichloromethane. The combined organics were washed with brine (10 mL), dried over potassium carbonate, filtered, and concentrated to 0.120 g of the piperidine as a thick oil. To a solution of this compound in 5 mL of dichloromethane was added 0.132 g of the acid intermediate prepared in Example 21 Step B, 0.055 g of HOBT, 0.102 g of EDC and stirred for 18h. The reaction mixture was diluted with 25 mL of ether and washed with 15 mL of 0.05N HCl, saturated sodium bicarbonate solution (15 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 20 g of silica gel with CH_2Cl_2-acetone (5:1) as eluent gave 0.094 g of the desired product.

^{1}H NMR ($CDCl_3$, 400MHz) δ 8.60 (s, 2/3H), 8.50 (s, 1/3H), 7.70 (d, 2/3H), 7.60 (d, 1/3H), 7.35 (d, 2/3H), 7.30 (d, 1/3H), 7.26-7.00 (m, 5H), 6.90 (t, 11/3H), 6.40 (d, 2/3H), 5.28-5.16 (m, 1H), 5.05 (bs, 1H), 4.41 (bd, 2/3H), 4.32 (bd, 1/3H), 3.78-3.65 (m, 2H), 3.56 (s, 2H), 3.55 (s, 1H), 3.50 (bd, 1H), 3.20 (dt, 1H), 3.15 (ddd, 1H), 2.75 (t, 1H), 2.42 (m, 1H), 1.18 (d, 2H), 1.24 (s, 4H), 1.50 (s, 2H), 1.48 (s, 4H), 1.42 (s, 9H), 1.30-1.18 (m, 1H), 1.10-0.90 (m, 11/3H), 0.03 (dt, 2/3H).

<u>Step C:</u> <u>N-[1(R)-[(1,2-Dihydro-[1-methoxycarbonyl-1-methyl-ethanesulfonyl]-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide trifluoroacetate</u>

A solution of 0.094 g of the intermediate from Step C was treated with 1 mL of dichloromethane and 1 mL of trifluoroacetic acid for 30 min., evaporated to dryness and triturated with ether to give 0.082 g of the desired product.

^{1}H NMR (CD_3OD, 400MHz) δ 7.70 (d, 2/3H), 7.60 (d, 1/3H), 7.35 (d, 2/3H), 7.30 (d, 1/3H), 7.26-7.00 (m, 5H), 6.90 (t, 11/3H), 6.40 (d, 2/3H), 5.28-5.16 (m, 1H), 5.05 (bs, 1H), 4.41 (bd, 2/3H), 4.32 (bd, 1/3H), 3.78-3.65 (m, 2H), 3.56 (s, 2H), 3.55 (s, 1H), 3.50 (bd, 1H), 3.20 (dt, 1H), 3.15 (ddd, 1H), 2.75 (t, 1H), 2.42 (m, 1H), 1.18 (d, 2H), 1.24

(s, 4H), 1.50 (s, 2H), 1.48 (s, 4H), 1.30-1.18 (m, 1H), 1.10-0.90 (m, 11/3H), 0.03 (dt, 2/3H).

EXAMPLE 39

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-3-amino-3-methyl-butanamide hydrochloride

Step A: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-3-amino-3-methylbutanamide

To a suspension of 1.14 g of 1,2-dihydro-1-methanesulfonylspiro-[3H-indole-3,4'-piperidine] hydrochloride (prepared as described in Step A of Example 18 (method 1)) in 50 mL of dichloromethane was added 0.80 mL of N-methylmorpholine, 1.00 g of N-tBOC-D-tryptophan, 0.80 g of HOBT, and 1.20 g of EDC and stirred at RT for 18h. The reaction mixture was diluted with 100 mL of ether and washed with 50 mL of 0.05N HCl, 50 mL of saturated sodium bicarbonate solution, dried over $MgSO_4$, and concentrated.

A solution of the above intermediate in 50 mL of ethyl acetate at 0°C was treated with HCl (g) for 2 min. and then stirred for 1h. Dry ether (50 mL) was added, and the precipitated solid was collected by filtration. The yield was 1.44 g.

To 0.86 g of the amine hydrochloride in 30 mL of dichloromethane was added, 0.24 mL N-methylmorpholine, 0.36 g of HOBT, 0.56 g of EDC, and stirred overnight. The reaction mixture was diluted with 100 mL of ether, and washed with 0.05N HCl (50 mL), 50 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatography of the residue over 20 g of silica gel with CH_2Cl_2-acetone (5:1) as the eluent gave 0.74 g of the desired product.

To a solution of 0.74 g of the above intermediate in 5 mL of ethyl acetate at 0°C was bubbled in dry HCl gas for 2 min. and stirred for 30 min. Ether was added to completely precipitate the

product. The solid was filtered and washed with ether under nitrogen, and dried to give 0.57 g of the desired product.
^{1}H NMR (CD_3OD, 400MHz) δ 7.69 (d, 2/3H), 7.55 (d, 1/3H), 7.37-6.90 (m, 5H), 6.82 (bt, 11/3H), 6.43 (d, 2/3H), 5.31-5.18 (m, 1H), 4.40 (bd, 2/3H), 4.30 (bd, 1/3H), 3.63-3.38 (m, 4H), 3.22-3.05 (m, 2H), 2.83-2.75 (m, 1H), 2.80 (s, 1H), 2.74 (s, 2H), 2.63 (dd, 1H), 2.55-2.43 (m, 2H), 2.20 (bd, 1H), 1.70-1.53 (m, 1H), 1.38 (2H), 1.36 (s, 2H), 1.35 (s, 1H), 1.34 (s, 1H), 1.18 (bd, 1H), 1.20-0.94 (m, 11/3H), 0.03 (dt, 2/3H).

EXAMPLE 40

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-[3-[2(R)-3-dihydroxylpropyl]-amino]-3-methylbutanamide hydrochloride

Step A: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-[3-[2(R)-3-dihydroxylpropyl]-amino]-3-methylbutanamide hydrochloride

To a solution 0.30 g of the compound obtained in Step B of Example 39 in 5 mL of dry methanol was added 1.5 g of anhydrous sodium acetate, 0.30 g (R)-1,2-isoprpylidene-glyceraldehyde (*Tetrahedron* **1985**, *41*, 3117) and stirred for 1h. A THF solution of sodium cyanoborohydride (8.7 mL of 1M solution) was added and stirred for 18h. The reaction mixture was diluted with 20 mL of water and extracted with dichloromethane (3X10 mL). The combined organics were washed with saturated sodium bicarbonate solution (10 mL), dried over K_2CO_3, and concentrated. Flash chromatography of the residue over 10 g of silica gel with CH_2Cl_2-methanol (98:2) gave 0.146 g of the reductively aminated compound.
^{1}H NMR ($CDCl_3$, 400MHz) δ 8.70-8.40 (m, 2H), 7.63 (d, 2/3H), 7.55 (d, 1/3H), 7.37 (t, 1H), 7.32 (d, 1/3H), 7.28 (d, 2/3H), 7.20-6.95 (m, 41/3H), 6.52 (d, 2/3H), 5.20-5.08 (m, 1H), 4.55-4.24 (m, 3H), 4.10 (t, 2/3H), 4.05 (t, 1/3H), 3.80-3.70 (m, 1H), 3.70-3.50 (m, 4H), 3.30-3.10

(m, 2H), 2.84 (s, 1H), 2.80 (s, 2H), 2.80-2.70 (m, 2H), 2.68-2.45 (m, 1H), 2.37 (s, 2H), 1.70 (t, 2/3H), 1.52 (bd, 1/3H), 1.44 (s, 2H), 1.43 (s, 1H), 1.35 (s, 2H), 1.33 (s, 1H), 1.25 (s, 3H), 1.33 (s, 6H), 1.20-1.05 (m, 2H), 0.90-0.65 (m, 1/3H), 0.30 (dt, 2/3H).

Step B:

A solution of 0.146 g of the above intermediate was stirred in 3 mL of methanol and 0.100 mL of concentrated hydrochloric acid for 30 min. The reaction mixture was evaporated to dryness and the solid was washed with ether and dried to give 0.109 g of the desired material.

^{1}H NMR (400MHz, CD_3OD) δ 7.63 (d, 2/3H), 7.55 (d, 1/3H), 7.41 (d, 2/3H), 7.38 (d, 1/3H), 7.32 (d, 1/3H), 7.26 (d, 2/3H), 7.21-7.10 (m, 4H), 7.08-7.00 (m, 21/3H), 6.63 (d, 2/3H), 5.25 (dd, 2/3H), 5.19 (dd, 1/3H), 4.36 (bd, 2/3H), 4.30 (bd, 1/3H), 3.92-3.83 (m, 1H), 3.80-3.50 (m, 6H), 3.28-3.10 (m, 3H), 3.05-2.95 (m, 2H), 2.90 (s, 1H), 2.86 (s, 2H), 2.78-2.55 (m, 4H), 1.83-1.65 (m, 1H), 1.43 (s, 2H), 1.39 (s, 2H), 1.37 (s, 1H), 1.32 (s, 1H), 1.36-1.20 (m, 1H), 0.04-0.18(m, 22/3H), -0.08 (dt, 2/3H).

EXAMPLE 41

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-[3-[2(R)-hydroxylpropyl]-amino]-3-methylbutanamide hydrochloride

Step A: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-[3-[2(R)-hydroxylpropyl]-amino]-3-methylbutanamide hydrochloride

To 0.26 g of the intermediate from Step B of Example 39 was added 5 mL of dry methanol, 1.5 g of anhydrous sodium acetate, freshly prepared 0.10 g of 2(R)-(tetrahydropyranyl)oxy-propionaldehyde and stirred for 1h at room temperature. A THF solution of

sodium cyanoborohydride (8.5 mL of 1M solution) was added and stirred for 18h. The reaction mixture was diluted with 10 mL of saturated sodium bicarbonate solution and extracted with dichloromethane (2X15 mL). The combined organics were washed with brine (10 mL), dried over K_2CO_3, and concentrated. Flash chromatography of the residue over 10 g of silica gel with CH_2Cl_2-methanol (98:2) as eluent gave 0.219 g of the desired product.

The above material was stirred in 3 mL of dry methanol with 0.10 mL of concentrated hydrochloric acid, evaporated to dryness, and the residue was triturated with ether to give 0.174 g of the title compound as a pale yellow foam.

^1H NMR (400MHz, CD_3OD) δ 7.63 (d, 2/3H), 7.55 (d, 1/3H), 7.41 (d, 2/3H), 7.38 (d, 1/3H), 7.32 (d, 1/3H), 7.26 (d, 2/3H), 7.21-7.10 (m, 4H), 7.08-7.00 (m, 21/3H), 6.63 (d, 2/3H), 5.25 (dd, 2/3H), 5.19 (dd, 1/3H), 4.36 (bd, 2/3H), 4.30 (bd, 1/3H), 3.92-3.83 (m, 1H), 3.80-3.50 (m, 4H), 3.28-3.10 (m, 3H), 3.05-2.95 (m, 2H), 2.90 (s, 1H), 2.86 (s, 2H), 2.78-2.55 (m, 4H), 1.83-1.65 (m, 1H), 1.43 (s, 2H), 1.39 (s, 2H), 1.37 (s, 1H), 1.32 (s, 1H), 1.36-1.20 (m, 1H), 1.28 (d, 3H), 0.04-0.18 (m, 22/3H), -0.08 (dt, 2/3H).

EXAMPLE 42

N-[1(R)-[[3-oxospiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl]carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide trifluroracetate

Step A:

To 0.165 g of the acid intermediate prepared as described in Step B of Example 19 in 10 mL of CH_2Cl_2 was added 0.095 g of 3-oxospiro[isobenzofuran-1(3H),4'-piperidine], 0.067 g of HOBT, and 0.110 g of EDC and stirred at room temperature for 4h. The reaction mixture was poured into 10 mL of CH_2Cl_2, and washed with 20% aqueous citric acid (5 mL), saturated sodium bicarbonate solution (5 mL), dried over $MgSO_4$, and concentrated. Flash chromatography of

the residue over 10 g of silica gel with hexane-acetone (3:1) as the eluent gave 0.234 g of the coupled product.

To a solution of 0.024 g of the above intermediate in 1 mL of CH_2Cl_2 was added 1.0 mL of trifluoroacetic acid and maintained at room temperature for 30 min. The volatiles were evaporated and the residue was triturated with ether to give 21 mg of the title compound as a solid.

^{1}H NMR (CD_3OD, 400MHz) δ 7.85 (d, 1/2H), 7.80 (d, 1/2H), 7.63 (t, 1/2H), 7.54-7.40 (m, 21/2H), 7.35-7.20 (m, 51/2H), 7.06 (d, 1H), 6.58 (d, 1/2H), 5.25-5.15 (m, 1H), 4.93 (s, 1H), 4.69 (bd, 1H), 4.55-4.40 (m, 2H), 4.14 (bd, 1H), 3.70-3.40 (m, 2H), 3.18-3.10 (m, 1H), 2.13 (dt, 1H), 2.90-2.75 (m, 2H), 2.70-2.50 (m, 2H), 1.47 (s, 1.5H), 1.46 (s, 1.5H), 1.44 (s, 1.5H), 1.43 (s, 1.5H),.

EXAMPLE 43

N-[1(R)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamide hydrochloride

This compound was prepared from 2(R)-N-t-butoxycarbonyl-5-phenylpetanoic and 1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine] hydrochloride using chemistry described for the preparation of compound in Example 18.

FAB MS Calc. for $C_{28}H_{38}N_4O_4S$:MW = 526.2; found m/e = (m+1) 527.9

EXAMPLE 44

N-[1(R)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-phenymethylthio)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: N-[1(R)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-phenymethylthio)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

This compound was prepared from the commercially available N-t-BOC-S-benzyl-D-cysteine and 1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine] hydrochloride using chemistry described for the preparation of the compound in Example 18.

FAB MS Calc. for $C_{27}H_{36}N_4O_4S_2$: MW = 544.7; found m/e = (m+1) 548.5.

EXAMPLE 45

N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(2'-pyridomethyloxy)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-hydroxyl-carbamic acid 1,1-dimethylethyl ester

To a solution of N-t-BOC-(D)-serine (56 mg, 274 mmole) in 2.5 mL of THF at room temperature was added 1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine] hydrochloride (prepared from Example 18, Step A, 83 mg, 0.274 mmole), triethylamine (45 mL, 0.33 mmole), HOBt (44 mg, 0.33 mmole), and EDC (63 mg, 0.33 mmole). After 3 hours, the mixture was diluted with ethyl acetate and then washed sequentially with water and brine. The organic layer was dried over sodium sulfate, filtered and

concentrated. The residue was purified by MPLC (silica gel, 100% ethyl acetate) to give 112 mg (90%) of the title compound.

Step B: N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(2'-pyridomethyloxy)ethyl] carbamic acid 1,1-dimethylethyl ester

To oil free sodium hydride (prepared from 60% oil dispersion of sodium hydride by washing with hexanes (3X), 9 mg, 0.21 mmole), in 0.3 mL of THF was added 2-picolyl chloride (16 mg, 0.1 mmole) in 0.3 mL of DMF. After 5 minutes, the intermediate obtained from Step A (45 mg, 0.1 mmole) was added to the reaction mixture. The mixture was stirred at room temperature for two hours and then diluted with ether. The ether layer was washed with water (5X), brine and dried over sodium sulfate. After purification (Preparative-TLC, silica gel, 100% ethyl acetate), 16 mg of the title compound was isolated (29%).

^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): 8.53 (m, 1 H), 7.77-6.83 (m, 7 H), 5.75 (m, 1/2 H), 4.98 (m, 2 H), 4.67 (m, 2 1/2 H), 4.25 (m, 1/2 H), 4.10 (m, 1/2 H), 3.91-3.67 (m, 4 H), 3.17 (m, 1 H), 2.91 (s, 3/2 H), 2.89 (s, 3/2 H), 2.79 (m, 1 H), 1.95-1.69 (m, 4 H), 1.42 (s, 9/2 H), 1.41 (s, 9/2 H).

Step C: N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(2'-pyridomethyloxy)-ethyl]-2-amino-2-methylpropanamide trifluoroacetate

A solution of the intermediate obtained from Step B (16 mg, 0.029 mmole) in 0.5 mL trifluoroacetic acid was stirred at room temperature for 1/2 hour and then concentrated. To a solution of this residue in 1 ml chloroform was added t-butyloxycarbonyl-α-methylalanine (6.5 mg, 0.032 mmole), HOBt (4.3 mg, 0.032 mmole), triethylamine (10 ml, 0.064 mmole), and EDC (6 mg, 0.032 mmole). After 12 hours at room temperature, the mixture was diluted with methylene chloride and then washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The

residue was purified by Preparative-TLC (silica gel, 100% ethyl acetate). The purified compound was concentrated. To the residue was added trifluoroacetic acid at room temperature. After 1 hour, the mixture was concentrated to give the title compound (5.3 mg). ^{1}H NMR (400 MHz, CD_3OD, mixture of rotamers): 8.70 (br. s, 1 H), 8.30 (m, 1 H), 7.84 (m, 1 H), 7.77 (m, 1 H), 7.36 (m, 1 H), 7.24 (m, 1 1/2 H), 7.06 (m, 1 1/2 H), 5.24 (t, 6 Hz, 1 H), 4.86 (m, 2 H), 4.56 (d, 13 Hz, 1 H), 4.08 (m, 1 H), 3.95 (m, 4 H), 3.36 (m, 1 H), 2.97 (s, 3/2 H), 2.96 (s, 3/.2 H), 2.01-1.78 (m, 4 H), 1.63 (s, 3/2 H), 1.61 (s, 3/2 H), 1.59 (s, 3/2 H), 1.58 (s, 3/2 H).

EXAMPLE 46

N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(2'-pyridothio)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(2'-pyridothio)ethyl] carbamic acid 1,1-dimethylethyl ester

To oil free sodium hydride (600 mg, 7.5 mmole) suspension in 20 mL DMF was added N-t-BOC-D-cysteine (1.2 g, 5.4 mmole) in 20 mL DMF at -10°C. The mixture was warmed to room temperature and stirred for addition an hour. A solution of 2-brompyridine (0.514 mL, 5.4 mmole) in 10 mL DMF was added to the reaction mixture. After heating for 20 hours at 80°C. To this reaction mixture was added CuI (1.03g, 5.4 mmole) and stirred at the same temperature for another 20 hours. The mixture was cooled to room temperature and poured into 0.5 N hydrochloric acid and extracted with ether. The ether layer was filter though Celite, dried over sodium sulfate and concentrated. The residue was purified by MPLC (silica gel, methylene chloride/methanol=10/1). To the purified compound (170 mg, 0.57 mmole) in methylene chloride was added 1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine] hydrochloride

(prepared from Example 18, Step A, 172 mg, 0.57 mmole), triethylamine (95 mL, 0.68 mmole), HOBt (92 mg, 0.68 mmole), and EDC (130 mg, 0.68 mmole) and reacted according to the procedure described in Example 45, Step A to give the title compound (310 mg, 99%).

Step B: N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(2'-pyridothio)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Prepared from the intermediate obtained from Step A (290 mg, 0.53 mmole) by the TFA deprotection procedure. This gave the title compound (102 mg).

^{1}H NMR (400 MHz, CD_3OD, mixture of rotamers): 8.45(dd, 5, 1 Hz, 1 H), 7.61 (m, 1 H), 7.39-7.05 (m, 6 H), 5.27 (m, 1 H), 4.52 (t, 12 Hz, 2H), 4.01 (m, 3 H), 3.80 (m, 1 H), 3.45 (m, 1 H), 2.98 (s, 3 H), 2.90 (m, 1 H), 2.10 -1.79 (m, 4 H), 1.63 (s, 3/2 H), 1.60 (s, 3/2 H), 1.59 (s, 3/2 H), 1.58 (s, 3/2 H). FAB-MS: 532.7 (M+1).

EXAMPLE 47

N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(cyclohexylthio)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: N-t-Boc-cyclohexylcysteine

To a solution of cyclohexylmercaptan (1 mL, 8.18 mmole) and methyl 2-acetamidoacrylate (1.29 g, 9 mmole) in THF was added a catalytic amount of sodium hydride at room temperature. After 7 days, the reaction was concentrated. A solution of the residue in 20 mL 6 N hydrochloric acid was refluxed for 4 hours and cooled to room temperature. The resulting solution was allowed to stand for 12 hours and filtered. The solids were dried under vacuum. To a mixture of this hydrochloric acid salt in 1 N sodium hydroxide solution (15 mL) was added di-t-butyl dicarbonate (1.68 g, 7.7 mmole) in 15 mL 1,4-dioxane.

After 12 hours, the mixture was poured into 0.5 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over sodium sulfate. After filtration and concentration, the title compound was isolated in 92% yield (2.23 g).

Step B: N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(cyclohexylthio)ethyl] carbamic acid 1,1-dimethylethyl ester

Prepared from the intermediate obtained from Step A (303 mg, 1.0 mmole) by the procedure described in Example 45, Step A to give the title compound (420 mg) in 76% yield.

Step C: N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(cyclohexylthio)ethyl] -2-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methyl-propanamide

A solution of the intermediate obtained from Step B (420 mg, 0.76 mmole) in 5 mL trifluoroacetic acid was stirred at room temperature for 1/2 hour and then concentrated and dried. To a solution of this residue in 10 mL chloroform was added t-butyloxy-carbonyl-α-methylalanine (170 mg, 0.84 mmole), HOBt (113 mg, 0.84 mmole), triethylamine (116 mL, 0.84 mmole), and EDC (160 mg, 0.84 mmole). After 12 hours at room temperature, the mixture was diluted with methylene chloride and washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by MPLC (silica gel, hexanes/ethyl acetate=1/1) to give the title compound (430 mg) in 89%.

Step D: N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(cyclohexylthio)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

A solution of the intermediate obtained from Step C (35 mg, 0.055 mmole) in 0.5 mL trifluoroacetic acid was stirred at room

temperature for 1/2 hour and then concentrated to give the title compound (33 mg).
^{1}H NMR (400 MHz, CD3OD, mixture of rotamers): 7.38 (d, 8 Hz, 1 H), 7.25-7.17 (m, 2 H), 7.06 (m, 1 H), 5.02 (m, 1 H), 4.52 (m, 1 H), 4.11 (m, 1 H), 3.97 (m, 2 H), 3.39 (m, 1 H), 3.02 (m, 1 H), 2.98 (s, 3 H), 2.90-2.71 (m, 3 H), 2.05-1.74 (m, 9 H), 1.62 (s, 3/2 H), 1.61 (s, 3/2 H), 1.60 (s, 3/2 H), 1.57 (s, 3/2 H), 1.32 (m, 5 H). FAB-MS: 537.9 (M+1).

EXAMPLE 48

N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(cyclohexylsulfinyl)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of the intermediate obtained from Example 47, Step C (35 mg, 0.055 mmole) in 1 mL methanol was added sodium periodate in 1 mL water at room temperature. After a couple of hours, the reaction mixture was diluted with ethyl acetate and washed with aqueous sodium sulfite solution. The organic layer was dried over sodium sulfate, filtered and concentrated. Deprotection of the residue by the trifluoroacetic acid procedure (Example 47, Step D) gave the crude product, which was purified by Preparative -TLC (silica gel, methylene chloride/methanol/ammonium hydroxide=10/1/0.1). The purified product was re-acidified with HCl in ether to give the title compound (21 mg).
^{1}H NMR (400 MHz, CD3OD, mixture of diastereomers and rotamers): 7.38 -7.04 (m, 4 H), 5.43 (m, 1 H), 4.50 (m, 1 H), 4.05 (m, 1 H), 3.96 (m, 2 H), 3.38 (m, 1 H), 3.13 (m, 1 H), 2.98 (s, 3 H), 2.90-2.71 (m, 3 H), 2.05-1.74 (m, 9 H), 1.62 (m, 6 H), 1.51-1.32 (m, 5 H). FAB-MS: 553.9 (M+1).

EXAMPLE 49

N-[1(R,S)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(cyclohexylsulfonyl)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of the intermediate obtained from Example 47, Step C (35 mg, 0.055 mmole) in 1 mL methanol was added OXONE in 1 mL water at room temperature. After a couple of hours, the reaction mixture was diluted with ethyl acetate and washed with aqueous sodium sulfite solution. The organic layer was dried over sodium sulfate, filtered and concentrated. To the residue was added trifluoroacetic acid by the procedure described in Example 47, Step D to give a crude product, which was purified by preparative -TLC(silica gel, methylene chloride/methanol/ammonium hydroxide=10/1/0.1). The purified product was re-acidified with HCl in ether to give the title compound (12 mg).

^{1}H NMR (400 MHz, CD_3OD, mixture of rotamers): 7.36 (dd, 7, 2 Hz, 1 H), 7.22 (m, 2 H), 7.06 (m, 1 H), 5.53 (m, 1 H), 4.51 (m, 1 H), 4.11 (m, 1 H), 3.95 (m, 2 H), 3.49 (m, 2 H), 3.38 (m, 1 H), 3.10 (m, 1 H), 2.98 (s, 3/2 H), 2.97 (s, 3/2 H), 2.91 (m, 1 H), 2.20-1.74 (m, 9 H), 1.62 (s, 3/2 H), 1.61 (s, 3/2 H), 1.58 (s, 3/2 H), 1.57 (s, 3/2 H), 1.51-1.32 (m, 5 H). FAB-MS: 569.9 (M+1).

EXAMPLE 50

N-[1(R)-[spiro[benzo[b]thiophene-3(2H),4'-piperidine]-1'-yl carbonyl-2-indole-3-yl)ethyl-2-amino-2-methylpropanamide hydrochloride

Step A: 1-[(1,1-dimethylethoxy)carbonyl]-3-hydroxy-4-methylene-1,2,5,6-tetrahydropyridine

To a suspension/solution of methyltriphenylphosphonium iodide (30 g, 74 mmole) in 150 mL of THF was slowly added butyllithium (2.5 N, 25.5 mL, 63.7 mmole) at 0°C. After stirring an hour at room temperature, N-t-BOC protected 4-piperidone (prepared

from 4-piperidone monohydrate hydrochloride by the procedure described in Protective Groups in Organic Synthesis T. W. Greene, John Wiley and Sons, NY. 1981.) in 50 mL of THF was added to reaction mixture at room temperature slowly. This reaction was stirred for 2 hours and filtered. The filtrate was concentrated and purified (MPLC, silica gel, hexanes/ethyl acetate=10/1) to give the Wittig product (7.9 g) in 82% yield.

To a suspension of selenium dioxide/silica gel (prepared according to the procedure described in *Chem. lett.* **1981**, 1703) in 30 mL methylene chloride was added t-butyl hydroperoxide (1.23 mL). After 15 minutes, the Wittig product (0.72 g, 3.69 mmole) in 5 mL of methylene chloride was added. The cloudy solution was stirred for 3 hours and filtered though Celite. The filtrate was washed with water, brine and dried over sodium sulfate. The organic layer was concentrated and purified by flash chromatography (hexanes/ethyl acetate=4/1) to give the title compound in 52% yield (0.41 g).

<u>Step B:</u> <u>1-[(1,1-dimethylethoxy)carbonyl]-4-chloromethyl-1,2,5,6-tetrahydropyridine</u>

The intermediate obtained from Step A (400 mg, 1.88 mmole) was dissolved in 10 mL benzene and thionyl chloride (165 ml, 2.26 mmole) was added and heated to 60°C for 25 minutes. The resulting mixture was poured into $NaHCO_3$ (aq.) and extracted with ether. The ether layer was dried over magnesium sulfate and concentrated to give title compound (333 mg, 77%).

<u>Step C:</u> <u>1-[(1,1-dimethylethoxy)carbonyl]-4-[[(2-bromophenyl)-thio]methyl-1,2,5,6-tetrahydropyridine</u>

The intermediate obtained from Step B (330 mg, 1.43 mmole) was dissolved in 10 mL of acetone and 2-bromothiophenol (172 ml, 1.43 mmole) and potassium carbonate (390 mg, 2.86 mmole) were added. The reaction mixture was heated to 60°C for an hour and then filtered though silica gel (100% ether). The organic layer was concentrated and purified by flash chromatography (silica gel,

hexanes/ethyl acetate=10/1) to give the title compound in 84% yield (460 mg).

Step D: 1'-[(1,1-dimethylethoxy)carbonyl]-spiro[benzo[b]thiophene-3-(2H),y'-piperdine

The intermediate obtained from Step C (450 mg, 1.17 mmole) was dissolved in 60 mL of benzene and AIBN (10 mg) and tributyltin hydride (644 mL, 2.39 mmole) were added. This mixture was refluxed for 2 hours and concentrated. The residue was dissolved in ether and bromine was added till the reaction solution turned to a brownish color. To this brownish solution at room temperature was added DBU (650 mL) in dropwise manner. The resulting cloudy solution was filtered though silical gel and washed with ether. The ether solution was concentrated and the residue was purified by radial chromatography (silic gel, hexanes/ethyl acetate=10/1) to give title compound (157 mg) in 43% yield.

Step E: N-[1(1R)-[spiro[benzo[b]thiophene-3(2H), y'-piperdine]-1'-yl)carbonyl]-2-(indole-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

A solution of the intermediate obtained from Step D (50 mg, 0.164 mmole) in 0.5 mL of TFA was stirred at room temperature for 1/2 hour and then concentrated. The residue was diluted with chloroform and washed with $NaHCO_3$ (aq.). The organic layer was dried over sodium sulfate, filtered and concentrated to give free amine (32 mg) in 95%. A solution of free amine (5.1 mg, 0.025 mmole) in 1 ml chloroform was added the intermediate obtained from Example 21 Step C (9.2 mg, 0.0246 mmole), HOBt (4.0 mg, 0.0295 mmole) and EDC (5.6 mg, 0.0295 mmole) at room temperature. After 12 hours, the reaction was poured into water and extracted with chloroform. The chloroform layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by Preparative -TLC (silica gel. hexanes/ethyl acetate=1/1) to give a colorless foam (13 mg, 94%). The

title compound was obtained from this colorless foam according to the procedure described in Example 18, Step C.
^1H NMR (400 MHz, CD_3OD) mixture of rotamers: δ 7.62 (d, 8 Hz, 2/3 H), 7.54 (d, 8 Hz, 1/3 H), 7.39 (d, 8 Hz, 2/3 H), 7.35 (d, 8 Hz, 1/3 H), 7.19-7.00 (m, 6 1/3 H), 2.62 (m, 1H), 1.72-1.65 (m, 2 1/3 H), 1.61 (s, 4H), 1.50 (s, 2H), 0.94 (m, 1H), 0.10 (m, 2/3 H). FAB-MS 477 (m+1).

EXAMPLE 51

Step A: 1',2-Dimethylspiro[isoindolin-1-one-3,4'-piperidine]

To a stirred solution of 2-methylisoindolin-1-one (1.47 g, 10 mmol, available from Aldrich chemical company) and mechlorethamine hydrochloride (2.9 g, 15 mmol) in DMF (50 mL) at 0° under Ar, was slowly added potassium hydride (35% in mineral oil, 4.5 g, 40 mmol). The reaction mixture was then slowly warmed to room temperature and stirred for additional 3 hours. TLC (60% ethyl acetate in hexane) showed reaction was complete. The mixture was slowly poured on to ice, and it was extracted with ethyl acetate six times. The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography eluting with a solvent gradient of 5-10% methanol in dichloromethane to provide 1.17 g of product.
^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J= 1.5 Hz, 6.5 Hz, 1H), 7.81 (d, J=7.1 Hz, 1H), 7.50-7.40 (m, 2H), 3.03 (s, 3H), 2.95-2.90 (m, 2H), 2.71 (dt, J= 2.6 Hz, 11.4 Hz, 2H), 2.46 (s, 3H), 2.31 (dt, J=4.7 Hz, 13 Hz, 2H), 1.44 (dd, J=1.6 Hz, 13 Hz, 2H).
FAB-MS calc. for $C_{14}H_{18}N_2O$, 230; found 231 (M+H).

Step B: 2-Methylspiro[isoindolin-1-one-3,4'-piperidine]

The demethylation procedure was according to Tidwell and Buchwald, J. Org. Chem. 1992, 57, 6380-6382. To a stirred solution of the product from Step A (1.0 g, 4.35 mmol) in 1,2-dichloroethane (10 mL) at 0° was added 1-chloroethyl chloroformate (0.56 mL, 5.2 mmol) and the mixture was stirred for 20 min.. Methanol (10 mL) was added

and the resulting mixture was refluxed for one hour. Evaporation and flash column purification eluting with 10-20% NH_4OH-MeOH(1:10) in chloroform yielded 0.63 g of product.

^1H NMR (400 MHz, CD_3OD): δ 8.02 (d, J=8 Hz, 1H), 7.85 (d, J= 8 Hz, 1H), 7.70 (t, J= 8 Hz, 1H), 7.60 (t, J= 8 Hz, 1H), 3.75-3.60 (m, 4H), 3.10 (s, 3H), 2.60-2.51 (m, 2H), 1.72 (br. d, J= 14 Hz, 2H).

EI MS calc. for $C_{13}H_{16}N_2O$, 216; found 301 (M^+, 5%), 216 (M^+), 185, 160.

Step C: 2-Methylspiro[isoindolin-1-one-3,4'-piperidine]-1'-carboxylic acid, 1,1-dimethylethyl ester

To a stirred solution of 2-methylisoindolin-1-one (100 mg) in DMF (2 mL) was added excess KH in mineral oil at 0° under Ar. After 5 min., bis(2-bromoethyl)*t*-butyl carbamate (300 mg) was added and the mixture was stirred at room temperature for 1 h and heated at 80° overnight. The mixture was poured on to ice, and it was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. The residue was purified by prep-TLC eluting with 60% ethyl acetate in hexane to provide 16 mg of product.

^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, J= 1.3 Hz, 5.8 Hz, 1H), 7.75 (d, J= 6.5 Hz, 1H), 7.54-7.40 (m, 2H), 4.35-4.10 (br. m, 2H), 3.02 (s, 3H), 2.14 (dt, J= 5.3 Hz, 13 Hz, 2H), 1.49 (s, 9H), 1.46-1.40 (m, 2H).

FAB-MS calc. for $C_{18}H_{24}N_3O_3$, 316; found 317 (M+H, 100%).

Step D: 2-Methylspiro[isoindolin-1-one-3,4'-piperidine]

The intermediate from Step C (16 mg) was treated with concentrated HCl and MeOH at room temperature for 2 hours and evaporated to yield the desired product.

All spectral data for this compound is the same as in step B.

Step E: N-[1(R)-[(2-Methylspiro[isoindolin-1-one-3,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[[(1,1-dimethylethyl-oxy)carbonyl]amino]-2-methylpropanamide

The compound was prepared according to standard peptide coupling technology from α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]-amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid (25 mg) and the product from Step B
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58, 8.44 (2 br. s, 1H), 7.80-7.15, 6.44 (m, d, J= 7.6 Hz, total 10H), 5.43-5.36, 5.22-5.15, (2m, 1H), 4.98 (br. s, 1H), 4.60-4.50 (br. m, 1H), 3.64-3.50 (br. m, 1H), 3.40-3.05, 2.72-2.64, (2m, 4H), 2.88, 2.51 (2s, 3H), 2.00-1.90 (m, 2H), 1.52, 1.51 (2s, 3H), 1.49 (s, 3H), 1.45, 1.44 (2s, 9H), 1.40-0.40 (several m, 2H).
FAB-MS calc. for $C_{33}H_{41}N_5O_5$, 587; found 588 (M+H), 532, 488.

Step F: N-[1(R)-[(2-Methylspiro[isoindolin-1-one-3,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

The title compound was prepared using HCl in ethyl acetate from the product of Step E.
^{1}H NMR (400 MHz, CD_3OD): δ 7.84-6.89 (m, 9H), 5.30, 5.15 (2 dd, 1H), 4.50-4.40 (m, 1H), 3.85-3.77 (m, 1H), 3.65-3.50 (m), 3.40-3.15 (m), 2.95, 2.58 (2s, 3H), 2.95-2.85 (m), 2.55-2.47 (m), 2.22-2.15 (m), 2.09-2.00 (m), 1.65, 1.64, 1.60 (3s, 6H), 1.50-1.20 (m), 1.15-1.05 (m), 0.9-0.8 (m), 0.61-0.52 (m).
FAB-MS calc. for $C_{28}H_{33}N_5O_3$, 471; found 472 (M+H).

EXAMPLE 52

N-[1(R)-[[1-[[[[[6-[[[4-azido-2-hydroxy-5-iodophenyl]carbonyl]amino]-hexyl]amino]carbonyl]methyl]sulfonyl]-2,3-dihydrospiro[3H-indole-3,4'-piperidin]-1'-yl]carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2methylpropanamide hydrochloride

To a solution of the commercially available N-hydroxy-succimidyl-4-azido-2-hydroxy-benzoate in 5 mL of CH_2Cl_2 was added 6-N-t-butoxycarbonyl-n-hexylamine hydrochloride and 0.10 mL of Hunig's base and stirred for 4h. The reaction mixture was evaporated to dryness and chromatorgraphed on 15 g of silica gel. Elution with

hexanes-ethyl acetate (2:1) gave 0.229 of the acylated product. To 29 mg of the above material was added 2 ml of THF and 2 mL of 0.01 M aqueous NaOH, 25 mg of potassium iodide. Chloramine-T (15 mg) was added and stirred for 30 min. The reaction was quenched with 2 mL of saturated sodium thiosulfate solution, diluted with 5 mL of 0.05N HCl and extracted with ethyl acetate (2X5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue (5 g silica gel) with hexane-ether (3:1) gave 26 mg of the iodonated material. Deprotection of the N-tBOC was carried out with 4M HCl in ethyl acetate to give 21.4 mg of the hydrochloride.

To solution of this material in 5 mL of CH_2Cl_2 was added 49 mg of the acid intermediate form Step A of Example 33, 0.016 mL of NMM, 19.8 mg of HOBT, and 29 mg of EDC and stirred for 18 h. The reaction was worked up and purified in the usual manner.

Once again deprotection of the N-tBOC group was carried with 4M HCl in ethyl acetate. This gave the title compound as a yellow-brown solid. This material was basified by dissolving in 2 mL of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (2X3 mL). The combined organics were dried over Na_2SO_4 and concentrated to the title compound.

^1H NMR ($CDCl_3$, 400 MHz) The compound exists as a 3:2 mixture of rotamers. δ 8.40-8.20 (m, 1H), 7.95 (s, 2/3H), 7.90 (s, 1/3H), 7.40-6.90 (m, 9 1/3H), 6.70 (s, 2/3H), 6.55 (m, 1H), 5.20-5.10 (m, 1H), 4.70-4.40 (m, 4H), 4.10-3.80 (m, 5H), 3.80-3.50 (m, 4H), 3.40-3.10 (m, 4H), 3.10-3.00 (m,1H), 2.70 (dt, 1H), 1.90-1.20 (m, 14H), 1.30 (s, 6H).

EXAMPLE 53

N-[1(S)-[(1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethylsulfonyl)ethyl]-2-amino-2-methyl-propanamide hydrochloride

Step A: N-[1(S)-[(1,2-Dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(phenylmethylsulfonyl)-ethyl]2-amino-2-methylpropanamide

A sample of N-[1(S)-[(1,2-dihydro-1-methylsulfonylspiro [3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(phenylmethylthio)ethyl]2-[[1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide (Example 44, Step C), 72 mg , was dissolved in 0.5 mL methanol and cooled in an ice bath. To this was added, dropwise, with stirring, a solution of 101 mg OXONE (TM) in 0.5 mL water. The reaction was monitored over several hours by TLC on silica gel GF plates, developed with 2:1 EtOAc: hexane; two more polar spots were observed to grow over time at the expense of the starting material. When the starting material was essentially gone, the reaction mixture was taken to near dryness under a nitrogen stream, and the residue extracted with chloroform. The $MgSO_4$ dried extract was subjected to preparative TLC on an 8" x 8" x 1,000 μ silica gel GF plate, developed with EtOAc: hexane; two bands were isolated. The less polar component was dissolved in 0.5 mLof anisole, cooled in an ice-bath, and treated with 0.5 mL of TFA. The reaction was stoppered and removed from the bath. After 30 minutes, the bulk of the TFA was removed under aspirator vacuum, and the bulk of the remaining anisole evaporated under a nitrogen stream. The residue was taken up in chloroform and shaken with 1 M K_2HPO_4, to which enough NaOH was added to give a pH > 9. The chloroform was then removed and the aqueous phase extracted several more times with chloroform, the combined organic phases dried with $MgSO_4$, and concentrated under reduced pressure to a gum. Preparative TLC on a silica gel GF plate with 0.5: 5: 95 Conc. NH_4OH:MeOH: $CHCl_3$ afforded the free base of the title compound. Calc. for $C_{27}H_{36}N_4O_6S_2$: MW = 576.7; found m/e = (m+1) 577.5.

Step B: N-[1(S)-[(1,2-Dihydro-1-methylsulfonylspiro [3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(phenylmethylsulfonyl)-ethyl]-2-amino-2-methylpropanamide hydrochloride

The hydrochloride salt of the compound from Step A above was produced using standard procedures described above affording the title compound.

EXAMPLE 54

Preparation of the two N-[1(S)-[(1,2-dihydro-1-methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethylsulfinyl)-ethyl]-2-amino-2-methylpropanamide hydrochlorides

Step A: N-[1(S)-[(1,2-Dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(phenylmethylsulfinyl)-ethyl]-2-amino-2-methylpropanamide

Subjecting the more polar band from Step A, Example 53, to the TFA/ anisole deblocking procedure described there, followed by the same preparative TLC workup, two bands are isolated, corresponding to the two diastereomeric sulfoxides expected.
For the less polar diastereomer: Calc. for $C_{27}H_{36}N_4O_5S_2$: MW = 560.7; found m/e = (m+1) 561.7.

For the more polar diastereomer: Calc. for $C_{27}H_{36}N_4O_5S_2$: MW = 560.7; found m/e = (m+1) 561.7.

Step B: N-[1(S)-[(1,2-Dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-2-(phenylmethylsulfinyl)-ethyl]-2-amino-2-methylpropanamide hydrochloride

The title compound is obtained by substituting either of the compounds isolated from Step A above for the compound prepared in Step A, Example 53 for Step B, Example 53,

EXAMPLE 55

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate

This compound was prepared by the treating the free base obtained in Example 18, Step C, with methane sulfonic acid. The title compound was obtained by recrystallizing it from ethyl acetate-ethanol-water. m.p. = 166°-168°C.

EXAMPLE 56

2,3,3a,4,6,6a-hexahydro-2-oxo-1H-thieno[3,4-d]imidazole-4(S)-pentanoic acid-6-[[[[[1'-[[(29R)-[[2-amino-2-methyl-1-oxopropyl]-amino]-3-(phenylmethyloxy)-1-oxopropyl]-2,3-dihydrospiro[3H-indole-3,4'-piperidin]-1'-yl]sulfonyl]methyl]carbonyl]amino]hexyl ester trifluoroacetate

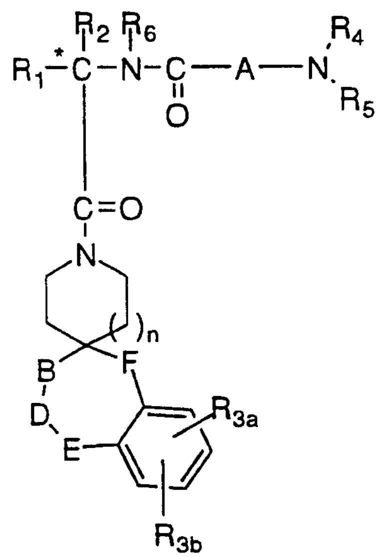
To a solution of 0.108g of the intermediate prepared in Example 33 step A in 5mL of CH_2Cl_2 was added 20mg of 6-amino-hexanol, 28mg of HOBT, and 42mg of EDC and stirred for 4h. the reaction mixture was diluted with 10mL of CH_2Cl_2 and washed with 0.5N HCl (5mL), satureated aqueous $NaHCO_3$ (5mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10g silica gel) with CH_2Cl_2-acetone (1:1) as eluent.

To 56.2mg of the above intermediate in 2mL of CH_2Cl_2 and 2mL of DMF was added 23mg of biotin, 14mg of DMAP, 28mg of EDC and stirred for 18h. The reaction was worked up in the ususal manner. Purification of the residue by flash chromatography over 5g of silica gel with CH_2Cl_2-acetone (1:1) as the eluent gave 22mg of the biotin conjugate. Deprotection of the N-tBOC was carried out in CH_2Cl_2-TFA to give 18.9mg of the title compound as a white solid. ^1H NMR ($CDCl_3$, 400MHz) The compound is a 3:2 mixture of rotamers. d 8.45-8.23 (m, 1H), 7.9 (s, 1H), 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.00 (dt, 2/3H), 6.80 (d, 1/3H), 5.21-5.14 (m, 1H), 4.60-

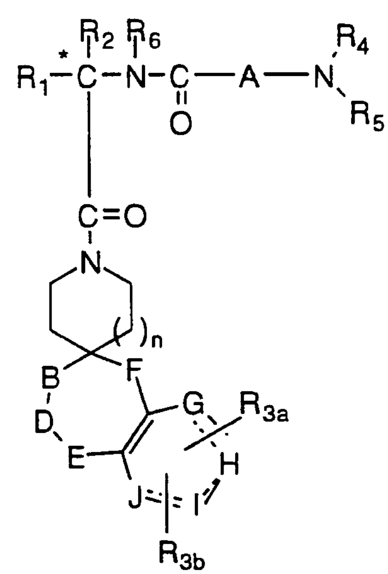
4.42 (m, 4H), 4.28 (bt, 1H), 4.15-4.00 (m, 6H), 3.85-3.70 (m, 2H), 3.20-3.10 (m, 3H), 2.90 (dd, 1H), 2.83 (dt, 1H), 2.70 (d, 1H), 2.40-2.25 (m, 2H), 2.00-0.60 (m, 18H), 1.62 (s, 3H), 1.60 (s, 3H).

WHAT IS CLAIMED IS:

1. A compounds of the formula;



Formula I



Formula II

R_1 is C_1-C_{10} alkyl, aryl, aryl (C_1-C_6 alkyl) and C_3-C_7 cycloalkyl (C_1-C_6alkyl) or C_1-C_5alkyl-K-C_1-C_5 alkyl, aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl), C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl) where K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, OC(O), C(O)O, or $-CR_2=CR_2-$ or $-C\equiv C-$ where the aryl groups are defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)_mR_{2a}$, 1 to 3 OR_{2a} or $C(O)OR_{2a}$ and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 OR_2, methylenedioxy, $S(O)_mR_2$, 1 to 2 CF_3, OCF_3, nitro, $N(R_2)(R_2)$, $N(R_2)C(O)R_2$, $C(O)OR_2$, $C(O)N(R_2)(R_2)$, $SO_2N(R_2)(R_2)$, $N(R_2)S(O)_2$ aryl or $N(R_2)SO_2R_2$;

R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

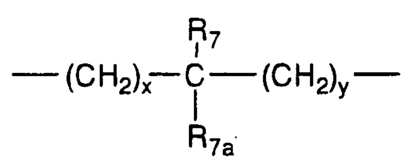
R_{2a} is hydrogen or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently hydrogen, halogen, C_1-C_6 alkyl, OR_2, cyano, OCF_3, methylenedioxy, nitro, $S(O)_mR$, CF_3 or $C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

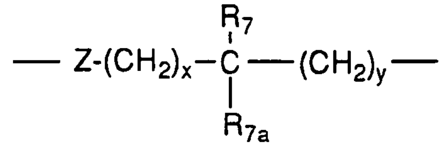
R_4 and R_5 are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form $-(CH_2)_rL_a(CH_2)_s-$ where L_a is $C(R_2)_2$, O, $S(O)_m$ or $N(R_2)$, r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



where x and y are independently 0-3;
Z is N-R_2 or O;

R_7 and R_{7a} are independently hydrogen, C_1-C_6 alkyl, OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR_2, 1 to 3 fluoro, $S(O)_mR_2$, $C(O)OR_2$, C_3-C_7 cycloalkyl, $N(R_2)(R_2)$, $C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently $C(R_8)(R_{10})$, O, C=0, $S(O)_m$, or NR_9, such that one or two of B,D,E, or F may be optionally missing to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be $C(R_8)(R_{10})$ or C=O only when one of the remaining B, D, E and F groups is simultaneously O, S(O)m or NR_9; B and D or D and E taken together may be $N=CR_{10}$- or $CR_{10}=N$ or B and D or D and E taken together may be $CR_8=CR_{10}$ provided one of the other of B and E or F is simultaneously O, $S(O)_m$ or NR_9;

R_8 and R_{10} are independently hydrogen, R_2, OR_2, $(CH_2)_q$ aryl, $(CH_2)_q$ $C(O)OR_2$, $(CH_2)_q$ $C(O)O(CH_2)_q$ aryl or $(CH_2)_q$ (1H-tetrazol-5-yl) and the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 OR_2 or 1 to 2 $C(O)OR_2$;

R_9 is R_2, $(CH_2)_q$ aryl, $C(O)R_2$, $C(O)(CH_2)_q$ aryl, SO_2R_2, $SO_2(CH_2)_q$ aryl, $C(O)N(R_2)(R_2)$, $C(O)N(R_2)(CH_2)_q$ aryl, $C(O)OR_2$, 1-H-tetrazol-5-yl, SO_3H, $SO_2NHC{\equiv}N$, $SO_2N(R_2)$aryl, $SO_2N(R_2)(R_2)$ and the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 OR_{2a}, $O(CH_2)_q$ aryl, 1 to 2 $C(O)OR_{2a}$, 1 to 2 $C(O)O(CH_2)_q$ aryl, 1 to 2 $C(O)N(R_{2a})(R_{2a})$, 1 to 2 $C(O)N(R_{2a})(CH_2)_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $C(O)NHSO_2R_{2a}$, $S(O)_mR_{2a}$, $C(O)NHSO_2(CH_2)_q$ aryl, $SO_2NHC{\equiv}N$, $SO_2NHC(O)R_{2a}$, $SO_2NHC(O)(CH_2)_q$aryl, $N(R_2)C(O)N(R_{2a})(R_{2a})$, $N(R_{2a})C(O)N(R_{2a})(CH_2)_q$ aryl, $N(R_{2a})(R_{2a})$, $N(R_{2a})C(O)R_{2a}$,

$N(R_{2a})C(O)(CH_2)_q$ aryl, $OC(O)N(R_{2a})(R_{2a})$, $OC(O)N(R_{2a})(CH_2)_q$ aryl; $SO_2(CH_2)_qCONH$-$(CH_2)_wNHC(O)R_{11}$, where w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

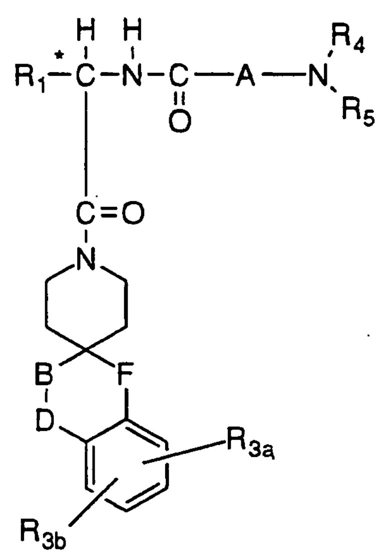
m is 0, 1 or 2;

n is 1 or 2;

q can optionally be 0, 1, 2, 3, or 4; and

G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that atleast one is a heteroatom and one of G, H, I or J may be optionally missing to afford 5 or 6 membered heterocyclic aromatic rings; and pharmaceutically acceptable salts and individual diastereomers thereof.

2. A compound of Claim 1 which is:



Formula III

where R_1 is C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl), C_3-C_6 cycloalkyl (C_1-C_4 alkyl), (C_1-C_4 alkyl)-K-(C_1-C_4 alkyl), aryl(C_0-C_5alkyl)-

K-(C_1-C_4 alkyl), (C_3-C_7cycloalkyl)(C_0-C_5 alkyl)-K-(C_1-C_4alkyl) where K is O, $S(O)_m$, $-CR_2=CR_2-$ or $-C\equiv C-$; or $N(R_2)C(O)$ where R_2 and the alkyl groups may be further substituted by 1 to7 halogen, $S(O)_mC_1$-C_4alkyl, OR_2 or $C(O)OR_2$ and the aryl groups may be further substituted by C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 OR_2, CF_3, OCF_3, methylenedioxy, $S(O)_mR_2$, $SO_2N(R_2)(R_2)$, $N(R_2)SO_2R_2$ or $C(O)OR_2$;

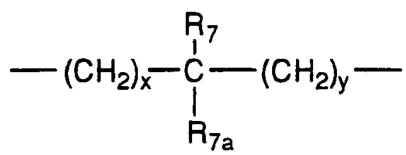
R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_7cycloalkyl, and, if two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_4-C_6 cyclic ring optionally including 1 to 2 heteroatoms selected from oxygen, sulfur or NR_{2a};

R_{2a} is hydrogen or C_1-C_6 alkyl;

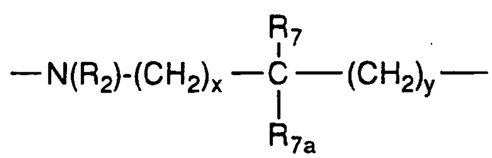
R_{3a} and R_{3b} are independently hydrogen, halogen, C_1-C_4 alkyl, OR_2, methylenedioxy, nitro, $S(O)_mC_1$-C_4alkyl, CF_3 or $C(O)OR_2$;

R_4 and R_5 are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 2 hydroxy, 1 to 2 C_1-C_6 alkanoyloxy, 1 to 2 C_1-C_6 alkyloxy or $S(O)_m$(C_1-C_4 alkyl);

A is :



or



where x and y, are independently 0, 1, or 2; R_7 and R_{7a} are independently hydrogen, C_1-C_4 alkyl, substituted C_1-C_4 alkyl where the substituents are from 1 to 3 fluoro or imidazolyl, phenyl, indolyl, $S(O)_mC_1$-C_4alkyl $C(O)OR_2$ or R_7 and R_{7a} can independently be joined to one or both of the R_4 and R_5 groups to form alkylene bridges between the teminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 3 carbon atoms;

B, D and F are independently $C(R_8)(R_{10})$, C=O, O, $S(O)_m$ or NR_9 such that one of B, D or F may be optionally missing to provide a 5 or 6 membered ring and provided that one of B, D and F is $C(R_8)(R_{10})$ or C=O only when one of the remaining B, D and F groups is simultaneously O, $S(O)_m$ or NR_9;

R_8 and R_{10} are independently hydrogen, R_2, OR_2, $(CH_2)_q$ aryl, $(CH_2)_qC(O)OR_2$, $(CH_2)_qC(O)O(CH_2)_q$ aryl $(CH_2)_q$ (1H-tetrazol-5-yl) and the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_4 alkyl, 1 to 3 OR_2 or 1 to 2 $C(O)OR_2$;

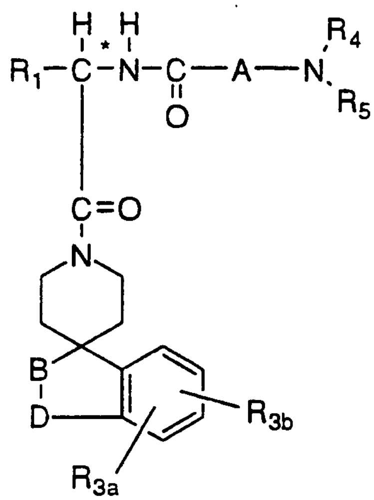
R_9 is R_2, $(CH_2)_q$ aryl, $C(O)R_2$, $C(O)(CH_2)_q$ aryl, SO_2R_2, $SO_2(CH_2)_q$ aryl, $C(O)N(R_2)(R_2)$, $C(O)N(R_2)(CH_2)_q$ aryl, 1-H-tetrazolyl-5-yl, $SO_2NHC{\equiv}N$, $SO_2N(R_2)$ aryl, $SO_2N(R_2)(R_2)$ and the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_2 alkyl and the R_2 may be optionally substituted by 1 to 2 OR_{2a}, $O(CH_2)_q$ aryl, 1 to 2 $C(O)OR_{2a}$, $C(O)N(R_{2a})(R_{2a})$, $S(O)_mR_{2a}$, 1-H-tetrazol-5-yl, $C(O)NHSO_2R_{2a}$, $C(O)NHSO_2(CH_2)_q$ aryl, $N(R_{2a})C(O)N(R_{2a})(R_{2a})$ or $N(R_{2a})C(O)N(R_{2a})(CH_2)_q$ aryl and the aryl may be optionally substituted by 1 to 2 OR_{2a}, 1 to 2 halogen, 1 to 2 C_1-C_4 alkyl,

$C(O)OR_{2a}$ or 1-H-tetrazol-5-yl; $SO_2(CH_2)_w$ $CONH(CH_2)_w$ $NHC(O)R_{11}$, where w = 1-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0,1, or 2;
q is 0, 1, 2 or 3; and
the aryl group is phenyl, napthyl, pyridyl, thienyl, indolyl, thiazolyl or pyrimidinyl,
and the pharmaceutically acceptable salts and individual diastereomers thereof.

3. A compound of Claim 2 where F is not present.

4. A compound of Claim 3 which is:



IV

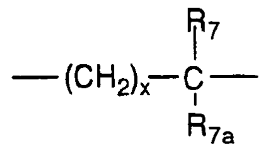
R_1 is C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl), C_5-C_6cycloalkyl (C_1-C_4 alkyl) or (C_1-C_4 alkyl)-K-C_1-C_2alkyl-, aryl(C_0-C_2alkyl)-K-(C_1-C_2 alkyl), C_3-C_6cycloalkyl (C_0-C_2alkyl)-K-(C_1-C_2alkyl), where K is O or $S(O)_m$, and the aryl groups may be further substituted by 1 to 2 C_1-C_4 alkyl, 1 to 2 halogen, OR_2, $C(O)OR_2$, CF_3 or $S(O)_mR_2$;

R_2 is hydrogen, C_1-C_4 alkyl, cyclo C_3-C_6alkyl, and, if two C_1-C_4 alkyls are present on one atom, they may be optionally joined to form a C_5-C_6 cyclic ring optionally including the heteroatoms oxygen or NR_{2a};

R_{2a} is hydrogen or C_1-C_4 alkyl;

R_{3a} and R_{3b} are independently hydrogen, halogen, C_1-C_4 alkyl, $C(O)OR_2$, hydroxy, C_1-C_4 alkoxy, $S(O)_mC_1$-C_4 alkyl or CF_3;

R_4 and R_5 are independently hydrogen, C_1-C_4 alkyl, substituted C_1-C_4 alkyl where the substituents may be 1 to 2 hydroxy or $S(O)_m$ (C_1-C_3alkyl);

A is: 

where x is 0 or 1;

R_7 and R_{7a} are independently hydrogen, C_1-C_3 alkyl; or R_7 and R_{7a} can independently be joined to one or both of the R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups to form 5 or 6 membered rings containing the terminal nitrogen;

B and D are independently $C(R_8)(R_{10})$, C=O, O, $S(O)_m$, NR_9 provided that one of B and D can be $C(R_8)(R_{10})$ or C=O only when the other of B and D is O, $S(O)_m$ or NR_9;

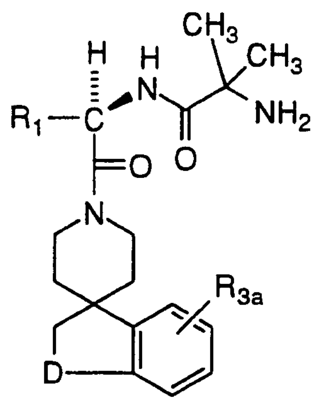
R_8 and R_{10} are independently hydrogen, R_2, OR_2, $(CH_2)_q$ aryl, and the aryl may be optionally substituted by 1 to 2 of halo, 1 to 2 C_1-C_4 alkyl, OR_2 or 1 to 2 $C(O)OR_2$;

R_9 is $C(O)R_2$, $C(O)(CH_2)_q$ aryl, SO_2R_2, $SO(CH_2)_q$ aryl, $C(O)N(R_2)(R_2)$, $C(O)N(R_2)(CH_2)_q$ aryl and the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_2 alkyl and the R_2 may be optionally substituted by 1 to 2 of OR_{2a}, $O(CH_2)_q$ aryl, $C(O)OR_{2a}$, $C(O)N(R_{2a}(R_{2a})$, $S(O)_mR_{2a}$, 1-H-tetrazol-5-yl, $C(O)NHSO_2R_{2a}$, or $N(R_{2a})C(O)N(R_{2a})(R_{2a})$ and the aryl may optionally be substituted by 1 to 2 OR_{2a}, 1 to 2 halogen, 1 to 2 C_1-C_2 alkyl, $C(O)OR_{2a}$, 1-H-tetrazol-5-yl or $S(O)_mR_{2a}$;
$SO_2(CH_2)_qCONH(CH_2)_wNHC(O)R_{11}$ where w = 2-6 and R_{11} may optionally be biotin, aryl, and an aryl be optionally substituted by 1 to 2 OR_2, 1-2 halogen, azido, nitro;

m is 0, 1 or 2;

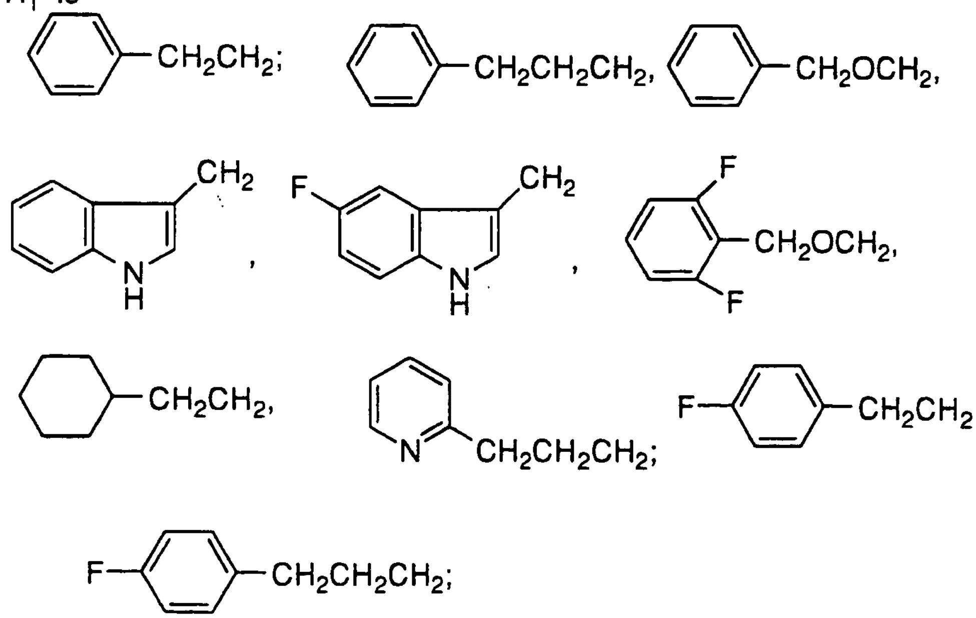
q can optionally be 0, 1, 2 or 3;
aryl is phenyl, napthyl, pyridyl, indolyl, thienyl or tetrazolyl and the pharmaceutically acceptable salts and individual diastereomers thereof.

5. A compound of Claim 1 have the formula:



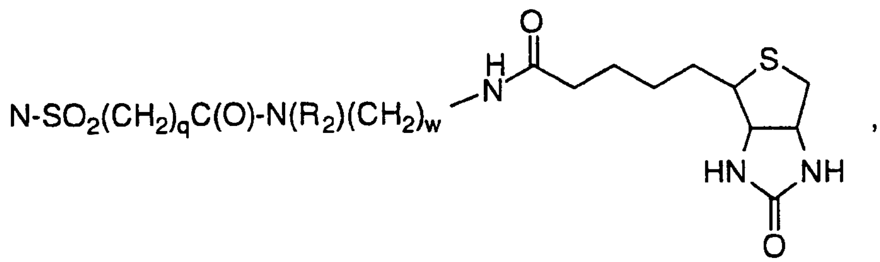
V

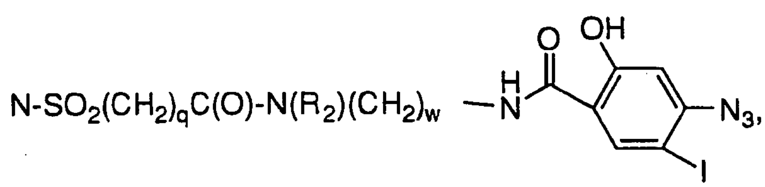
R1 is

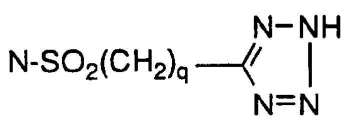


R3a is H, fluoro;

D is O, S, S(O)m, N(R2), NSO2(R2), NSO2(CH2)taryl, NC(O)(R2), NSO2(CH2)qOH, NSO2(CH2)qCOOR2, N-SO2(CH2)qC(O)-N(R2)(R2), N-SO2(CH2)qC(O)-N(R2)(CH2)wOH,







and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;

R2 is H, C_1-C4 alkyl;
m = 1, 2;
t is 0, 1, 2;
q is 1, 2, 3;
w is 2-6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

6. A compound of Claim 1 which is:
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

N-1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide; or

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

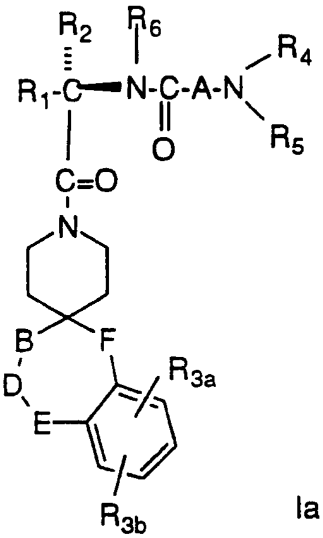
N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

N-[1(R)-[(1,2-Dihydro-1,1dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

and pharmaceutically acceptable salts thereof.

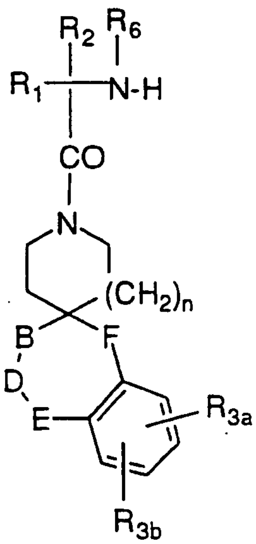
7. The compounds of Claim 1 which are



Ia

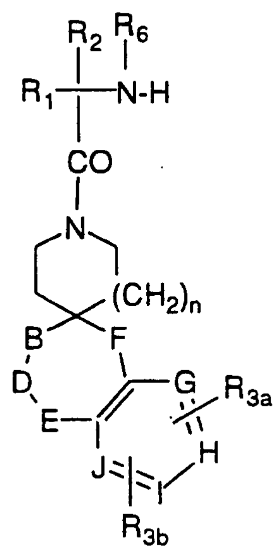
and where R1, R2, R3a, R3b, R4, R5, R6, A, B, D, E, F, G. H. I. J. and n are as defined as in Claim 1.

8. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:



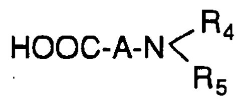
4

or

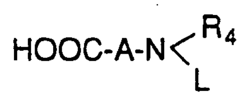


4a

with a compound having the formula

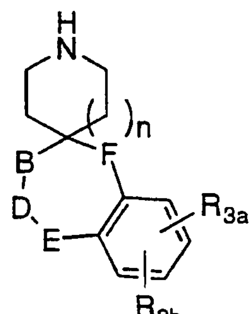


or

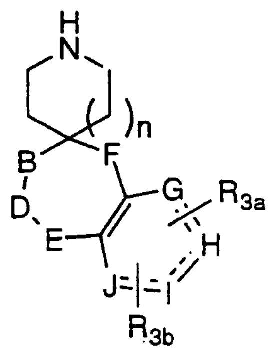


where R1, R2, R3a, R3b, R4, R5, R6, A, B, D, E, F, G, H, I, J and n are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

9. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:

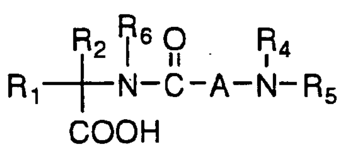


2



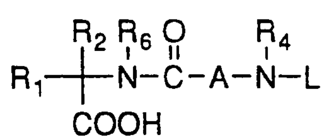
2a

with a compound having the formula



12

OR



12a

where R1, R2, R3a, R3b, R4, R5, R6, A, B, D, E, F, G, H, I, J and n are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

10. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of a compound of Claim 1.

11. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1.

12. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim I used in combination with other growth hormone secretagogues such as GHRP-6, GHRP-1, GHRP-2, growth hormone releasing factor (GRF), one of its analogs or IGF-1 or IGF-2.

13. A method for the treatment of osteoporosis which comprises treating a patient with osteoporosis with a bisphosphonate compound in combination with a compound of Claim 1.

14. The method of Claim 13 where the bisphosphonate compound is alendronate.

15. A composition for the treatment of osteoporosis which comprises an inert carrier, a bisphosphonate compound and a compound of Claim 1.

16. The composition of Claim 15 where the bisphosphonate compound is alendronate.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 93/11038

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07K5/02 C07K5/06 C07D471/10 A61K37/02 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 513 974 (MERCK & CO. INC.) 19 November 1992 see claims; examples ---	1,10-16
A	EP,A,0 144 230 (PFIZER LIMITED) 12 June 1985 see claims; examples -----	1,10-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 1994	28. 04. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 93/ 11038

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark : Although claims 10,13,14 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/US 93/11038

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0513974	19-11-92	US-A- 5206235	27-04-93
		AU-A- 1301292	24-09-92
		CN-A- 1066070	11-11-92
		WO-A- 9216524	01-10-92
EP-A-0144230	12-06-85	CA-A- 1263499	28-11-89
		JP-A- 60155194	15-08-85
		US-A- 4562197	31-12-85